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SUPPLEMENT NUMBER 14 ON WAR MEDICINE AND SURGERY:
Blast Injuries and Crush Injuries.

IMMUNIZATION AGAINST EPIDEMIC INFLUENZA WITH LIVING ATTENUATED VIRUS.[1]

By F. M. BURNET,

From the Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne.

DURING the past year active research on epidemic influenza has been in progress at the Walter and Eliza Hall Institute. Through the cooperation of army authorities it has been possible to study the disease as it occurs in military camps and to carry out some large-scale attempts at immunization. The results of an investigation of the influenza epidemic of May, 1942, have already been published.[(1)] The epidemic was of normal character and was due to an A type virus antigenically similar to the strain "Melbourne". It was first recognized in the last week of April and appears to have ended about the middle of June.

Arrangements to carry out immunization of a large proportion of the Australian troops who were at that time in Victoria had been made some time previously; but as a result of the unusually early appearance of the epidemic much of the immunization was done at a time when influenza was present in the camps.

Before this large-scale work was authorized, a fairly large preliminary experiment on army volunteers had been carried through, to determine the proportion of persons likely to show an effective antibody response and to confirm that the method was free from danger. A number of other aspects of influenza virus work arising out of these primary investigations have called for study.

A full report of the army immunizations has been submitted to the authorities concerned, and in this paper it is proposed to give only a general account of our experience, omitting most of the technical detail and all statements as to the numbers of men immunized or the units concerned. In order to provide a more general account of the position a brief description is given of some other aspects of influenza work in this laboratory. Throughout we have been concerned primarily with the intranasal method of immunization and with problems relevant to the method. This has led our work to develop along different lines from those being followed in American and English laboratories, where interest has centred on subcutaneous methods of immunization. In this paper no attempt will be made to cover adequately the progress made overseas in the development of these subcutaneous methods. The paper is intended only to serve as a progress report of work at the Walter and Eliza Hall Institute and to provide a background for the two papers on the intranasal method of immunization published elsewhere in this journal.

The Method of Intranasal Immunization.

The method of immunization used was to spray into each nostril egg fluid containing a high concentration of three living attenuated strains of influenza virus representing the main antigenic types. It had been shown in extensive preliminary work (Burnet and Foley,[(2)] and unpublished) that with repeated passage through chick embryos inoculated into the amniotic cavity, influenza A strains showed a progressive loss of pathogenicity for human beings. From the results of this work three strains, "Melbourne" 46th amniotic passage, "W.S." 100th amniotic passage and the type B strain "Lee" 40th amniotic passage, were chosen as suitable for use. "Seed" virus was prepared and stored in capillary tubes in a solid carbon dioxide refrigerator. All vaccine was made by diluting the seed virus 1:100 and inoculating it into the allantoic cavity of eggs of ten to twelve days' incubation. Ten-day eggs are to be preferred, owing to the absence of urate precipitation in the fluids. After two days' incuba-

[1] Work carried out with the aid of grants for research on virus diseases from the National Health and Medical Research Council and from Mr. E. Alec Cato.

tion at 35° C. the eggs were chilled and the allantoic fluid was harvested. About ten cubic centimetres of lightly turbid fluid of high virus content was obtained from each. This was checked for activity by Hirst's method and for freedom from bacterial contamination. Virus of each type was pooled and the whole was diluted with an equal volume of saline solution. The fluid was kept on ice until used, and any remainder was discarded after fourteen days.

The virus was administered by being sprayed with a de Vilbiss type atomizer into each nostril, about 0·25 cubic centimetre of virus being used for each subject. For large-scale work a power spray with a large low-pressure air reservoir was used. Nozzles were sterilized after each inoculation.

Administration of influenza virus vaccine by this method results in a significant rise of antibody in a considerable proportion of subjects. The results of an experiment made in February, 1942, with 107 soldier volunteers are shown graphically in Figures I, II and III. These indicate the changes in antibody level detected by the Hirst red-cell agglutination test against the three antigenic types used

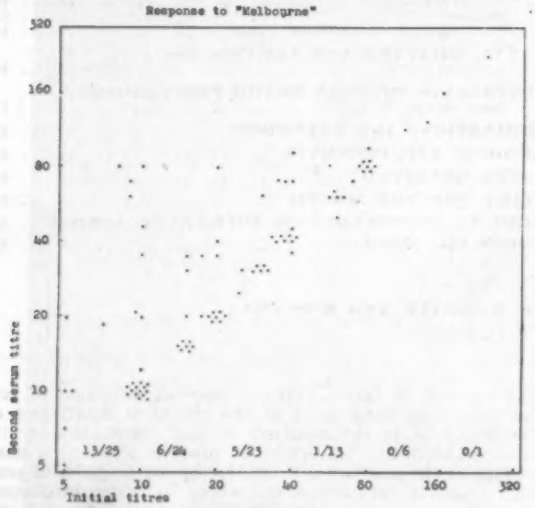


FIGURE I.

Antibody response as measured by Hirst tests in immunized volunteers. Each dot represents the initial (abscissæ) and second (ordinates) serum titre of one individual. All dots grouped on the line running diagonally therefore represent failures to show any antibody rise. Dots above and to the left of the diagonal indicate increase in antibody, the figures below representing the proportion in each group of initial levels which show a significant rise. Tested against "Melbourne" (A).

for immunization. The first amount of serum was prepared from blood taken at the time of spraying, the second from blood taken three weeks later. A similar set of results obtained with civilian volunteers in Adelaide will be found in the paper by Mawson and Swan.[3] The data from which Figures I, II and III were constructed may be summarized as follows.

1. For each type of virus, from 68% to 80% of the subjects showed no significant change in antibody level.

2. Rises in antibody level are shown by 20% to 32% of subjects; no significant falls in antibody level were observed.

3. The proportion of persons showing a rise in antibody level is greatest amongst those having the lower initial antibody levels.

4. A significant number of subjects showed an associated rise against both "Melbourne" and "W.S."; but there was no evidence of any significant association between responses to A and B types.

5. Of the 91 subjects whose serum was fully tested, 46 showed a rise regarded as significant against one or more components of the vaccine.

Taken at their face value, these results are considerably inferior to those obtained by American workers with subcutaneous inoculations of adequately high titre virus; but it must be remembered that the intranasal vaccine

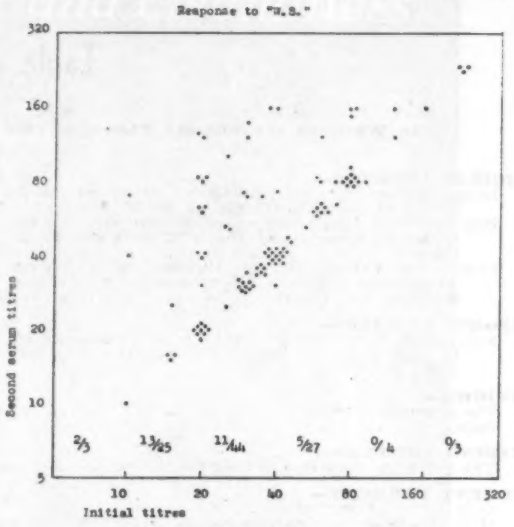


FIGURE II.

Antibody response as measured by Hirst tests in immunized volunteers. Each dot represents the initial (abscissæ) and second (ordinates) serum titre of one individual. All dots grouped on the line running diagonally therefore represent failures to show any antibody rise. Dots above and to the left of the diagonal indicate increase in antibody, the figures below representing the proportion in each group of initial levels which show a significant rise. Tested against "W.S." (A).

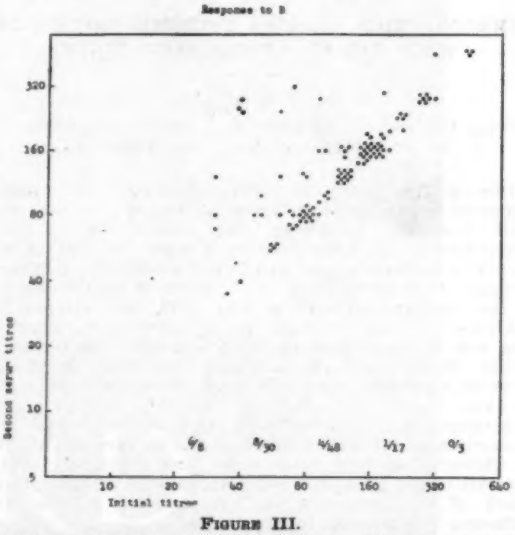


FIGURE III.

Antibody response as measured by Hirst tests in immunized volunteers. Each dot represents the initial (abscissæ) and second (ordinates) serum titre of one individual. All dots grouped on the line running diagonally therefore represent failures to show any antibody rise. Dots above and to the left of the diagonal indicate increase in antibody, the figures below representing the proportion in each group of initial levels which show a significant rise. Tested against "Lee" (B).

can be expected to "take" only in those subjects who are susceptible to influenza virus infection. It is a commonplace that even in the pandemic of 1918 about 70% of persons escaped clinical infection. Even with an "ideal"

vaccine of this type, one would not expect more than 30% to 50% of subjects to show a definite rise in antibody level against any one type. The existence of a real resistance in some persons to infection by attenuated strains is strikingly shown by the failure in most instances of repeated reinoculations to provoke a rise of antibody level in those subjects who failed to respond with such a rise to the first inoculation (Mawson and Swan[3]).

Symptoms are trivial or absent in the great majority of persons inoculated; but a proportion of subjects, varying from group to group, show more definite local signs with or without headache and slight malaise. Amongst soldiers in camp the number complaining of symptoms is smaller than amongst civilians. Of 107 men questioned in February, 1942, 65 stated that they had had no symptoms whatever after the inoculation, 24 described coryzal symptoms, most of which lasted only for a day or two, and there were a number of minor complaints probably unrelated to the inoculation. Although some tens of thousands of troops have been inoculated, no complaints have been received of any reactions sufficiently severe to interfere with training. Amongst civilians coryzal reactions are more frequent. In one large metropolitan hospital about 300 of the staff were immunized. The medical superintendent reported that about half showed some coryzal reactions, often with headache; the great majority of the reactions were mild, but three persons were away from work for two to four days. The only unsatisfactory feature of the symptomatology has been the occasional report of a "persistent cold" dating from the time of inoculation. We have had no opportunity to investigate any cases of this sort and have no direct evidence as to how often nasal sinusitis follows intranasal immunization or whether it occurs with any greater frequency than in an untreated population. On general grounds, it seems probable that when anatomical or bacteriological conditions in the nose, or both, predispose the subject to clinical sinusitis, the specific influenzal infection induced by the vaccine may on occasion act as a trigger-mechanism and induce it. The same possibility, of course, arises with every common cold; but until the position is clarified it must be admitted as a potential disadvantage of the intranasal method of immunization. It should be stressed, however, that nearly all the coryzal reactions after immunization last for only one or two days and are not followed by the mucopurulent stage characteristic of a common cold.

In only one unit of about 7,000 men was it possible to obtain any information as to the effect of immunization on the incidence of respiratory tract infection during a proved influenza epidemic. Immunization was being carried on in this unit during the period of influenza prevalence, and only two weeks were available in which (*a*) the immunized group had been inoculated more than one week previously, and (*b*) the influenza epidemic was still current. During these two weeks 4·4% of the immunized "reported sick" with some form of upper respiratory tract infection, as against 6·63% of those not immunized. This apparent 50% advantage of the immunized must be treated with reserve. The groups concerned were large, approximating 5,000 inoculated and 2,500 uninoculated men; but the division into groups was mainly determined by the availability of men at the time the immunization was carried out. The unimmunized, for instance, include most or all of those who were infected with influenza before or at the time of immunization. It has also not been possible to make a detailed analysis of the various infections included in the upper respiratory tract infection group of military records, and from the figures available there was a much smaller advantage of the immunized in regard to infections producing the typical influenza syndrome. The only conclusion that could be reached is that there was at most only a minor benefit in this epidemic, and that an assessment of the actual effect would have required a carefully devised statistical experiment. It should be stated that at the time immunization was started it was fully realized that no satisfactory experimental set-up was possible and that only indefinite conclusions were likely. There was always the possibility, however, that movements of troops or other circumstances might provide a clear-cut contrast in the behaviour of the immunized and the non-immunized.

The most important information obtained from the large-scale immunization was the demonstration that even in the very cold wet weather of May, 1942, when influenza was actually spreading in the camps, the intranasal method of immunization produced no serious acute reactions. The chief theoretical objection to the use of attenuated virus is the possibility that under field conditions spread from person to person may allow the attenuated virus to regain virulence. There is no indication from any source that such a change occurred either in May, when influenza was present, or in June and July, when it had disappeared.

The Use of Attenuated Virus in the Experimental Analysis of Resistance to Influenza.

Although the intranasal administration of attenuated virus has been developed wholly on account of its potential value as an immunizing method, it also provides a new experimental method for the analysis of resistance to influenza. The application of the method is exemplified in both the papers which accompany this communication.

Bull and Burnet[4] have found that three to six months after a primary attempt at immunization with influenza virus B, the great majority of subjects resist a second inoculation without evidence of antibody response. It was noted, too, that the two subjects who resisted the first attempt at immunization were also resistant to the second, and further, that the antibody level alone (Hirst method) was not a complete index of susceptibility or non-susceptibility. At the time of the second inoculation the group was as a whole more resistant than would have been judged by a comparison of antibody levels with the values at the time of the first inoculation.

In Mawson and Swan's experience, most of the subjects who resisted inoculation at the first trial also failed to show a rise in antibody level with subsequent tests. Both sets of experiments go to strengthen the view that resistance to infection by attenuated virus may well be a fairly definite index of resistance to natural infection. If this is so, one must not regard a failure to provoke a rise of antibody level in certain subjects as necessarily indicating a weakness of the method. It may have that significance; but equally well it may mean merely that the subject in question is not susceptible to influenza and does not need immunization.

We have encountered one group of forty persons who showed a strikingly lower proportion of positive antibody responses against both A and B types of virus than any of the other groups which have been reported. The subjects were fairly recent arrivals from overseas, and the reason for this difference from Australians has not been determined.

Nasal Factors in Relation to Influenza.

It is agreed that nasal fluid from normal adults has a power to inactivate influenza virus. Francis[5] regards this power as wholly a manifestation of small amounts of antibody, while Burnet, Lush and Jackson[6] regarded it as due to an enzyme-like agent. Current work in this institute has brought to light two more sets of facts, which appear to have a bearing on the question of the resistance of the nasal mucosa to infection by influenza virus. Beveridge and Burnet[7] have found that infective allantoic fluid, which has been inactivated by being boiled, can be used as material for an intradermal test for sensitivity to influenza virus products. In children there is a close correlation between skin sensitivity and evidence of past influenzal infection in the form of circulating antibody. In adults it is rare to find non-reactors, just as it is rare to find persons without detectable antibody in the blood. If low-grade allergic reactivity, as shown by this test, is present in the skin, a similar modified reactivity is to be expected in the nasal mucosa and in that of the lower respiratory passages. In Bull and Burnet's[4] paper is presented some direct evidence for the importance of allergic factors in determining whether response to

attenuated virus will be subclinical or associated with symptoms. No opportunity of applying these ideas to the study of clinical influenza during an epidemic has yet arisen; but such a study is clearly called for. The results may be particularly illuminating in regard to childhood infections, a phase of influenza study which has been seriously neglected.

The second set of facts is concerned with the effect of human tears on influenza virus. Burnet, Lush and Jackson[8] stated that tears had no inactivating effect on the virus when tests were made by inoculation of mixtures on the chorio-allantois or in mice. On reexamining the problem with the Hirst red-cell technique, Beveridge (unpublished) has found that tears are highly effective in inhibiting the specific agglutinating activity of any of the stock virus strains like "Melbourne" and "W.S." Tears diluted to 1:2,560 will, under standard conditions, inactivate the strain "Melbourne", and most old laboratory strains are inhibited at similar high dilutions. Tests against freshly isolated strains, still in the unmodified "human" state, however, reveal no inactivation, even with tears diluted only 1:10. The significance of this phenomenon has yet to be worked out; it may possibly be considerable.

The Nature of Attenuation in Virus Strains.

Our work with living virus vaccines has completely established the fact that influenza virus strains can be attenuated for human beings to almost any desired degree. In one instance it has been shown directly that a strain with only one ferret and one amniotic passage since isolation was highly virulent for susceptible subjects (Burnet and Foley[3]), but after forty amniotic passages only trivial or no symptoms were produced by the same strain (unpublished data).

An attempt has recently been made to elucidate the stages by which this transformation occurs during chick embryo passage. It was observed that when freshly isolated by amniotic inoculation in chick embryos, the virus (amniotic fluid) had an unusual type of agglutinating activity; guinea-pig red cells were agglutinated to a much higher titre than the standard fowl cells used by Hirst.

If the ratio between the two titres is expressed in the form $\frac{\text{titre with fowl cells}}{\text{titre with guinea-pig cells}}$ (F/G ratio), such recently isolated virus gives values like 15/160. If a stock laboratory strain is similarly tested, it will give an F/G ratio of the type 320/240. On investigation, it was found that unless special precautions were taken the original human virus in what we have called the O phase changed on passage to the derivative (D phase) with an F/G ratio of one or over. The change can be avoided and the virus maintained in the original O form by means of the method of passage at limiting dilutions. In this way it is possible to compare virus in the state in which it produces human influenza (O phase) with virus adapted to transfer in the laboratory (D phase). There are several well-defined differences between the two phases. The O form fails completely to multiply in the allantoic cavity of the chick embryo; it has little power to infect mice, but infects ferrets and guinea-pigs more readily than the D form, and it shows the non-susceptibility to the action of human tears previously mentioned. There are reasons to think that so long as the virus remains in the O phase it is of full virulence for human beings, and it is possible that a major degree of attenuation takes place when the O to D change occurs. These suggestions have not been tested experimentally, but there can be little doubt that work along these lines will make it possible to control the process of attenuation more closely.

Antibody in Relation to Resistance against Influenza.

There is a certain rough inverse correlation between the antibody level in the blood and susceptibility to influenza; but in every series of experiments published one finds a proportion of subjects with a high antibody level who go down with typical influenza. If one could obtain a method of determining by some indirect test whether or not a person was immune to influenza of a given type, the problem of devising the most satisfactory method of immunization would be greatly simplified. There are already four practical means of estimating specific influenza virus antibody in human serum—two *in vivo* tests by mouse inoculation or by titration on the chorio-allantois of the chick embryo, and two *in vitro* methods (complement fixation and Hirst's hæmagglutination method). No two of these tests give fully concordant results, and there is no agreement yet as to which of them most nearly reflects the resistance of the subject to infection by the corresponding type of influenza virus.

In this laboratory we have investigated a fifth method of antibody titration—inoculation into the allantoic cavity of the chick embryo (Burnet and Beveridge[2]). Like all the other methods, this one has certain individual characteristics which may be of value in particular problems. It is much more specific in differentiating between antibody corresponding to different subtypes of virus than any other test, and probably for the same fundamental reason it shows an extraordinarily sharp rise after the appropriate antigenic stimulus. Serum which before infection will neutralize only 10 or 100 infective doses of virus will neutralize 100,000,000 doses a fortnight after the infection. The method so far has been used only in a limited series of investigations; but it has already been shown that a high proportion (18/19) of the specimens of serum obtained from patients suffering from influenza had only insignificant amounts of antibody measured by this method, whereas 9/36 specimens of serum from unselected normal subjects from a similar population had significant amounts. Should further work confirm the present indication that the level of antibody detectable by this method is of particular significance in determining resistance to influenza, the task of devising improved methods of immunization would then become mainly one of finding the procedure which produced the largest and most broadly effective antibody response of the type detected by allantoic titration. Work along these lines has hardly been commenced, but it will be noted in the paper by Bull and Burnet that intranasal immunization with influenza B virus does in some instances at least give a satisfactory response of this type.

Discussion.

The possible lines along which attempts might be made to control or minimize the loss of life associated with an influenza pandemic like that of 1918-1919 have been discussed in the monograph by Burnet and Clark.[9] In the year since that discussion was prepared, the chief advance to be reported is the development by American workers (Hirst *et alii*[10] and Henle and Chambers[11]) of methods of concentrating virus from infected allantoic fluid, making possible a larger subcutaneous dosage of either living or killed virus. These larger doses undoubtedly raise the antibody level much more than the original preparations did. Since there is some evidence that a fairly effective resistance to experimental influenza virus infection is induced by unconcentrated allantoic fluid vaccine (Stokes and Henle[12]), the concentrated antigens should be of considerable value.

From the point of view of preparing rapidly very large amounts of immunizing material, however, the use of tenfold concentrated virus will require more than ten times the amount of material and skilled labour needed for the earlier type—a serious disadvantage if pandemic circumstances call for rapid action.

The great potential advantage of the intranasal method in such circumstances is its simplicity and the correspondingly smaller demands on time, skilled manpower and materials, always provided, of course, that an equally effective degree of immunity is produced. The results now published are at least promising. With regard to influenza B, it is hard to resist the conclusion, from the combined results of the Melbourne and Adelaide investigations, that a significant protective effect would probably be shown in an epidemic of that type. The more important problem of protection against influenza A presents greater

difficulties. It is thought that as yet unrecognized factors may be at work in determining the resistance of persons who since childhood have been periodically infected clinically or subclinically with the virus. It may be that continued efforts to improve the intranasal method of immunization will provide opportunities to recognize the nature of the other factors involved in resistance to influenza A.

On the negative side, the intranasal method has its own disadvantages and potential dangers. Our experience in the past winter showed that the proportion of severe reactions was extremely small; but in large-scale work there will always be some persons who have more or less unpleasant local reactions. The possibility that the immunizing infection will light up a bacterial infection in the nasal sinuses must also be considered.

A theoretical danger is the possibility that virulent influenza may be generated by passage from the attenuated strains in susceptible human beings. This has become much less cogent with the demonstration of the sharp genetic change from the epidemic O form to the D form. Until it is shown that this change is an irreversible one, however, the theoretical possibility remains. Both practical experience and epidemiological considerations suggest that the danger of its occurrence is infinitesimally small. Of more potential importance is the danger common to all living inocula of accidental contamination with some other organism, bacterial or virus. An automatic safeguard here is the fact that no human pathogenic viruses except the influenza viruses are known to multiply in the allantoic cavity of the chick embryo. Two viruses from acute diseases of fowls are the only others which multiply in this situation.

These various disadvantages would be of little significance in the face of a pandemic if the method were known to be effective in preventing serious influenza; but they do indicate that much has to be done before the method is suitable for routine use against the normal chances of winter influenza. But while the threat of pandemic influenza exists, as it must in wartime, it seems advisable to continue experimental attempts to perfect the method.

The possibility of passive immunization methods should not be forgotten, and in fact the greatest success yet claimed in preventing influenza is that of Smorodintseff, Gulanoff and Chalkina.[13] The Russian workers used hyperimmune horse serum given by inhalation in the form of a mist, about two cubic centimetres of serum to each person. The first inhalation was given at a time when an influenza epidemic was at its peak. A second inhalation was given ten to fifteen days afterwards. In the remainder of the epidemic period there were four cases in 501 treated persons (0·8%) in contrast to 150 cases in 1,825 controls (8·2%). The work in question needs confirmation on two points. In the first place, it should be established that inhalation of foreign serum into the lower respiratory passages does not provoke serious allergic reactions or sensitize persons to subsequent administrations. Secondly, the treated subjects were volunteers, the controls those who did not volunteer, and as in all such experiments in which a simple alternate choice of persons as subjects and controls is not adopted, there must be some doubt as to whether unrecognized factors did not have some share in the result. However, the question of the validity of their controls is carefully discussed by Smorodintseff *et alii*[13] and the reported results certainly provide a good case for the further investigation of the method.

Summary.

1. An account is given of the large-scale application in army units of a method of immunization against influenza by the intranasal administration of attenuated living influenza virus, types A and B.

2. Results of some recent Australian work on influenza are described and discussed in relation to the problems of immunization by living virus.

Acknowledgement.

This paper reviews work carried out in this institute by the following members of the virus department: W. I. B. Beveridge, Diana R. Bull, F. M. Burnet, Ellen Clark and S. E. Williams. I would again express my appreciation to Colonel Gordon Shaw and Professor P. MacCallum for making possible the investigation in army units, and to Colonel G. A. Penington and his officers for providing the statistics of respiratory infections in the unit referred to in the text.

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EXPERIMENTAL IMMUNIZATION OF VOLUNTEERS AGAINST INFLUENZA VIRUS B.[1]

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IN the course of our work on the immunization of human volunteers against influenza by the intranasal route, we have consistently found that results with influenza virus B are more regular than those obtained with type A strains. It has been shown both by Burnet[1] and by Mawson and Swan[2] that the level of circulating antibody (Hirst's method) is a fairly accurate index of susceptibility to experimental infection with living attenuated influenza virus B. The object of the present experiments was to extend this work, to test some modifications in the method of administering the virus and to determine whether a primary administration of virus produced resistance to a second administration some months later. It will be shown that of 23 subjects chosen for low antibody titre against influenza virus B, 21 showed a significant rise in antibody level after the primary administration of virus, while only two showed any rise

[1] Work carried out with the aid of grants for research on virus diseases from the National Health and Medical Research Council and from Mr. E. Alec Cato.

after the second administration three to six months later. Short of exposure to a natural epidemic or to experimental infection with fully virulent virus, this provides the best available evidence that a real resistance to infection is induced by the procedure.

TECHNIQUE.

Selection of Volunteers with Low Antibody Level.

A preliminary blood sample was taken from about 100 volunteers to select those whose serum, tested by Hirst's method, had a low antibody level against influenza virus B. To avoid the necessity of venepuncture, a method was developed in which only 0·05 cubic centimetre of blood was used; it was taken from the thumb into a calibrated capillary pipette. This was mixed with 0·475 cubic centimetre of saline solution, and after the clot had formed the red cells and fibrin were spun out in the centrifuge. The supernatant fluid then represented a 1:20 dilution of serum, and this was used as the initial dilution for titration in the usual way against a standard dilution of influenza virus B. Those subjects whose serum gave an end-point with serum dilutions of 1:80 or lower were selected as suitable for experiment.

Administration of Virus.

The virus was administered in the form of allantoic fluid from embryos inoculated with 39th amniotic passage of influenza virus B, as previously described (Burnet).[1] In addition to the normal method[2] of spraying with a hand atomizer, in which two pressures of the bulb were given to each nostril and one to the back of the throat, two other methods were used. It was thought possible that local vasoconstriction by adrenaline might result in a larger proportion of cells being primarily infected. The second method[3] was similar to the first, except that one cubic centimetre of a 1:1,000 solution of adrenaline (Parke, Davis and Company) was added to nine cubic centimetres of virus. Tests by allantoic inoculation showed that the adrenaline had no effect on the virus titre. In the third method[3] a second nasal spray was given about fifteen minutes after the first. It was thought that, in addition to introducing twice the amount of virus, this method might favour infection in other ways. The first administration by using up any free antibody on the surface of the nasal mucosa might allow more ready access of subsequently introduced virus to the susceptible cells. In addition, there was the possibility to be considered that the mild irritation caused by the first spray might alter the vascular status of the mucosa and so modify its susceptibility to infection. Actually no significant difference was observed in the results with the different methods of inoculation; but in order to make the test inoculation as severe as possible, the third method was used for the second series of virus administration after the three to six months' interval.

Demonstration of the Presence and Amount of Virus in the Nose Two Days after Inoculation.

Attempts were made to reisolate virus from the nose forty-eight hours after the virus had been administered. Nasal secretion was collected in a firmly rolled plug of cotton gauze, which was inserted into the nostril after this had been sprayed with a small amount of saline solution. These plugs were pressed up sufficiently far to cause mild irritation and to provoke a flow of secretion. When saturated, they were removed and the fluid was collected by wringing them between artery forceps. The fluid obtained was diluted by the addition of half its volume of nutrient broth, and it was then lightly spun to remove gross particles. Mice were inoculated intranasally with the unfiltered supernatant fluid, previous experiments having shown that the common bacterial contaminants in such material produced no pulmonary lesions.

The mice which were inoculated with material from the first group of volunteers were killed at the seventh day, and their lungs were examined for macroscopic lesions. Very few lesions, some of them of equivocal character, were obtained, and in the subsequent experiments the mice were tested for immunity. A fortnight after being inoculated with the nasal washings the mice were reinoculated with a 1:100 dilution of stock influenza B virus prepared from glycerolated mouse lung. All control and unimmunized mice given this inoculum either died specifically in six or seven days or were found to have gross three to four grade lesions when killed on the seventh day. Any mice which had either no lesions or lesions involving less than one-eighth of the total lung surface were regarded as immune. In some of these mice there were small grey lesions representing the effect of the original inoculum; but a majority had no such lesions.

In order to determine what amounts of virus could be detected by this method, a comparative titration of a sample of the virus used for the inoculation was made. The virus, allantoic fluid infected with 40th passage B virus, was titrated directly by the allantoic method. The same dilutions were then used to inoculate six mice intranasally for each dilution. As a test for immunity, these mice were reinoculated on the fourteenth day with virus from glycerolated mouse lung diluted to 1:100. Those mice surviving for seven days after this reinoculation were killed and examined. The results of this comparative titration test, which are given in Table I, show that the allantoic method is the more sensitive means of detecting virus. The mouse immunity method occasionally detects an amount of virus not much above one infective dose for the egg, but immunity is consistent only after 100 such doses.

TABLE I.

Comparative Titration of 40th Passage Influenza Virus B.[1]

Dilutions.	Titration Method.												
	Allantoic Titration.				Mouse Titration.								
					Test for Immunity.								Proportion Immune.
10^{-6}	−	−	−	−									
10^{-7}	+	+	−	−	4†	3+	3+	3	2+	2+			0/6
10^{-6}	+	+	+	+	4	4	3+	3	3	2			0/6
10^{-5}	+	+	+	+	4†	2−	1−	0	0	0			3/6
10^{-4}					0	0	0	0	0	0			6/6
Control mice ..					4†	4†	3+	3+	3	3			0/6

[1] All inoculations were in a volume of 0·05 cubic centimetre from the dilution shown; the diluent was ice-cold saline solution containing 10% normal horse serum. "+" = allantoic fluid from inoculated egg, which gives a positive response to the Hirst agglutination test. "−" = fluid which shows no agglutination. Mouse lung lesions are expressed by the usual convention; 4† means death at the seventh day with completely consolidated lungs; 3, 2 and 1 are diminishing degrees of consolidation. Under the "Test for Immunity" only recent lung lesions are recorded. Most of the immune mice showed small healing lesions from the primary inoculation.

Collection and Titration of Serum.

A blood sample was taken at the time of spraying of the nostrils and another three weeks later. The serum was separated, inactivated at 56° C. and stored in the refrigerator. Both specimens of serum were titrated simultaneously against standard allantoic fluid virus by the modified Hirst technique previously described (Burnet *et alii*[3]). The same procedure was carried out in regard to the reinoculations three to six months later, and in every instance the tests were repeated with all four samples of serum against the same virus. Titres are expressed as the serum dilution showing "+" agglutination when mixed with standard dilution influenza B virus.

A few samples were also tested for antibody by mouse inoculation or by allantoic inoculation of chick embryos (Burnet and Beveridge[4]).

EXPERIMENTAL RESULTS.

The results of these experiments are collected in Table II.

Symptoms.

As usual, we found difficulty in assessing the significance of minor symptoms. Most of the subjects had some symptom to report, but the majority of these were

TABLE II.

Results of Immunization with Attenuated Influenza Virus B followed by a Second Administration in Eleven to Twenty-four Weeks.

Serial Number and Name of Subject.	First Administration of Virus.					Interval between Inoculations. (Weeks.)	Second Administration of Virus.				
	Method of Administration.	Symptoms.[1]	Demonstration of Virus in Nasal Washings.[2]	Antibody Values.[3]	Extent of Antibody Rise.[3]		Method of Administration.	Symptoms.	Demonstration of Virus in Nasal Washings.	Antibody Values.	Extent of Antibody Rise.
1. McN.	1	− −	1/3	5–150	+ + + +	19	3	+ +	0/4	45–320	+ + +[4]
2. Pry.	1	− −	3/3*	10–65	+ + ±	24	3	± −	0/4	40–90	+[5]
3. Moo.	2	− −	1/4	10–75	+ + +	18	3	− −	0/4	100–100	−[5]
4. Hoy.	1	− −	1/3*	15–90	+ + ±	20	3	± −	0/4	75–90	±[5]
5. Per.	2	− −	0/4	15–100	+ + +	18	3	− −	0/4	140–150	−[5]
6. And.	1	− −	1/3*	15–120	+ + +	24	3	− −	0/4	120–120	−[5]
7. Bea.	3	± +	1/4	15–120	+ + +	14	3	± −	0/4	120–120	−[5]
8. Rob.	1	± −	0/3*	20–40	+	24	3	± −	0/4	38–40	−
9. Dol.	1	− −	0/3*	30–120	+ +	24	3	− −	0/4	70–75	−
10. Smy.	1	± −	0/3*	38–70	+	18	3	± −	0/3	70–70	−
11. Ing.	1	± −	2/3*	38–70	+	18	3	± +	0/4	70–70	−
12. Fon.	1	± −	1/3*	38–110	+ ±	17	3	± +	0/3	110–110	−
13. Sha.	1	− −	1/3*	40–40	−	17	3	± −	0/4	35–40	−
14. Hog.	1	± −	1/3	40–140	+ +	17	3	+ −	0/4	80–80	−
15. Jos.	1	± ±	1/3*	40–150	+ +	18	3	± −	0/2	100–120	−
16. Lin.	2	− −	0/4	40–160	+ +	11	3	± −	1/4	80–80	−
17. Dar.	2	− −	0/4	60–60	−	11	3	+ −	1/4	60–60	−
18. Mul.	1	− −	1/3	60–120	+	17	3	± −	0/4	120–120	−
19. Hoc.	3	± −	0/4	75–140	+	12	3	± −	0/4	−140	Probably −[7]
20. Gre.	3	± ±	2/4	75–140	+	12	3	± −	0/4	−150	Probably −[7]
21. Mur.	2	± ±	0/4	75–160	+	11	3	− +	0/4	140–140	−
22. Rod.	3	± ±	3/3	75–250	+ +	12	3	± −	0/4	150–160	−
23. Wes.	3	± −	0/3	75–320	+ +	12	3	± −	1/4	360–300	−

[1] The first symbol refers to local nasal symptoms, the second to general toxic symptoms. Local symptoms: "−"=no complaint, "±"=trivial discomfort, sneezing *et cetera*, "+"=definite nasal symptoms. General symptoms: "−"=no complaint, "±"=slight headache, "+"=definite headache, muscular pains, or fever.

[2] Numerator shows number of mice rendered immune (or where marked with asterisk, showing pulmonary lesions) after inoculation with nasal washings; denominator total number of mice inoculated.

[3] Figures show the values ascribed to initial and subsequent serum samples by Hirst titration. All four samples of serum were titrated at the same time. In the next column the amount of increase is roughly indicated by the number of "+'s", each "+" representing a difference of one tube in the comparable titration series; for example, "+"=twofold, "+ +"=fourfold, "+ + +"=eightfold increase.

[4] See text for details.

[5] Laboratory worker.

[6] First inoculation, symptoms atypical, inflamed cervical lymph nodes.

[7] Third sample unobtained.

trivial—sneezing, nasal obstruction or watery discharge. These are indicated in the table by the sign "±". A few had more definite local symptoms. Mild headache was relatively frequent, and five persons had some general toxic symptoms. One of these, McN. (second spray), had fairly severe symptoms, and this volunteer's reactions will be described separately in a later section. Symptoms were more often noted after the double spray than after either of the single spray methods (25 out of 30 as against 8 out of 18). There was no correlation between the intensity of symptoms and the extent of the rise in antibody level. Amongst those who showed an eight-fold or better rise of antibody level after the first inoculation, only one of five showed any symptoms at all. There is, in fact, a distinct suggestion from the results that persons with the smallest amounts of antibody show no symptoms, whereas those with higher amounts do. If the figures from both sets of sprayings are combined, two out of eight of those with an antibody level of 20 or below, and 30 out of 38 of those with an antibody level above 20, showed symptoms. This raises the interesting suggestion that for these attenuated strains at least the symptoms reported have a predominantly allergic basis.

Demonstration of Virus.

The reisolation results have been rather unsatisfactory, since on only two occasions have we found evidence of infection in all the mice inoculated. As the method is only just capable of detecting virus when a brisk rise in antibody level gives clear evidence of virus multiplication, negative results in individual instances are of no significance. If we compare the whole series of first inoculations with second inoculations, however, the differences are significant. Evidence of virus was found in nasal washings from 14 of 23 subjects given the first spray (7 of 13, if we use only the immunity test), but from only 3 of 23 in the second series. There was no clear correlation between the intensity of symptoms or the extent of the rise in antibody level and the reisolation of virus. In the first series it was isolated in seven cases among thirteen subjects showing symptoms, and in seven cases from ten subjects without symptoms. Of seven subjects showing a six-fold or better rise of antibody level, six gave evidence of virus in the nose; but amongst the others who showed a significant rise in antibody level, the virus was isolated in only seven instances in fourteen subjects, and virus was also isolated from one of the two who showed no rise in antibody level. In the second series the three isolations were all from subjects showing no rise in antibody level.

The numbers are insufficient to substantiate a suggestion that virus is more readily isolated from persons with low initial antibody level at the time of the first spraying. The figures for the different antibody levels are as shown in Table III. The trend is in the direction which would be expected on *a priori* grounds if the nasal exudate contains antibody in proportion to the serum content (Francis, 1941[6]).

TABLE III.

Relation between Isolation of Virus and Initial Antibody Level.

Initial Hirst Antibody Level.	Number of Subjects from whom Virus was Isolated.	Number of Subjects from whom Virus was not Isolated.
<10	4	0
−20	3	2
−40	5	3
−80	3	4

Changes in Antibody Content of Serum.

The changes in antibody content of the serum may be summarized as indicating that a significant rise followed the primary administration in 21 of 23 subjects, that the antibody titres were maintained or fell only slightly over the period of nine to twenty-one weeks before the next

blood sample was taken, and that in only two instances was there any significant rise after reinoculation. The difference in the type of response to the two series of inoculations is clearly seen in Figure I, which shows the initial and subsequent levels of antibody for each individual. Both sections of the figure are arranged with subjects having the lowest initial antibody level to the left-hand side. The numerals at the foot will allow the identification of the subjects from the list in Table II. Section I shows how the rise in antibody level is greatest in those with low initial levels. In Section II it will be seen that the only two subjects to show a significant rise in antibody level (numbers 1 and 2) had very low initial antibody levels (probably nil), and both showed a significant fall in the period between the first and second tests.

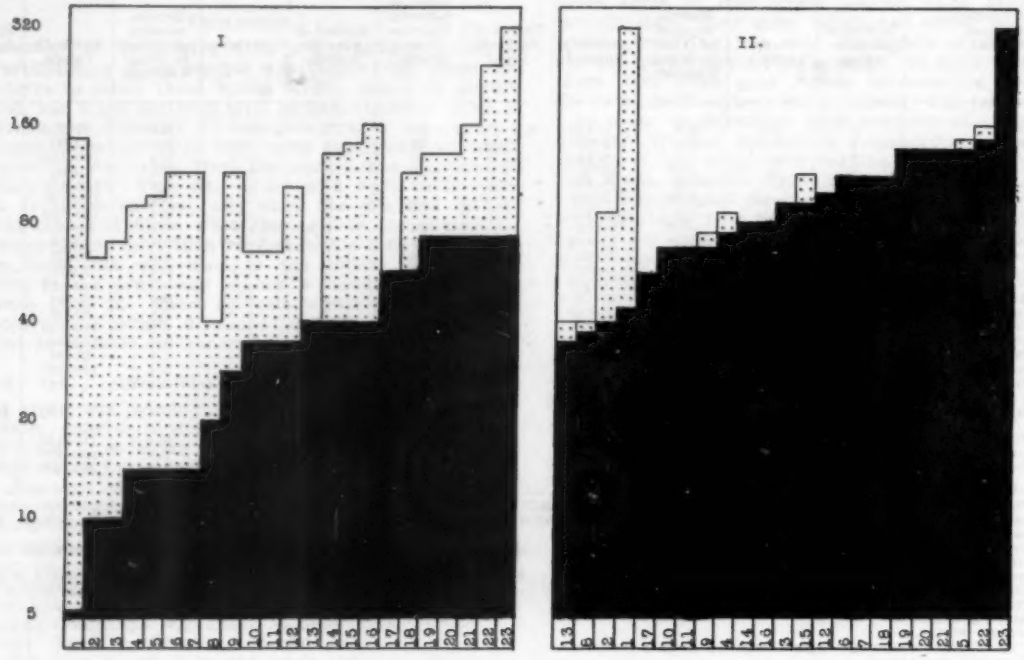


FIGURE I.

Antibody responses of volunteers to intranasal administration of influenza virus B. I. Response to primary administration. II. Response to a second administration three to six months later. Hirst antibody titres are shown vertically; each column represents one subject, and the columns are arranged in ascending order of initial antibody level. The upper limit of the blackened area represents the antibody titre before inoculation, while the stippled column gives a measure of the increase after inoculation. No decreases were observed.

TABLE IV.

Mouse Tests Against Dilute Influenza Viruses A and B.

Number and Subject.	Virus B/100.[1]	Virus M/100.[1]
1. McN. ..	4[6] 4[6] 3+	0 0 0
2. Pry. ..	4[7] 3+ 3+	0 0 0
3. Moo. ..	3+ 3 3	0 0 0
4. Hoy. ..	1+ 1 0	0 0 0
5. Per. ..	1 1 1	0 0 0
6. And. ..	1+ 1 1	0 0 0
7. Bea. ..	3 2 2	0 0 0
8. Rob. ..	1 0 0	0 0 0
9. Dol. ..	0 0 0	
10. Smy. ..	2 1 0	
11. Ing. ..	1− 0 0	
12. Fon. ..	0 0 0	
13. Sha. ..	0 0 0	
14. Hog. ..	1 1− 0	
15. Jos. ..	0 0 0	
16. Lin. ..	3 3 2	
17. Dar. ..	1− 0 0	
18. Mul. ..	2+ 2 1	
19. Hoc. ..	0 0 0	
20. Gre. ..	1+ 0 0	
21. Mur. ..	0 0 0	
22. Rod. ..	2+ 2 1+	
23. Wes. ..	0 0 0	
Controls	4[6] 4[7] 4[7]	4[6] 4[6] 4[6]

[1] Undiluted serum was mixed with 1 : 100 dilution of stock "Melbourne" (M) or "Lee" (B), and the mixtures inoculated intranasally in three mice each. Mouse lesions are expressed according to the usual convention.

Comparison of Mouse Titration of Antibody with Hirst Test Values.

In order to gain some information as to which of these subjects could be regarded as having initially no influenza B antibody whatever, the initial specimens of serum were tested in mice against a dose of virus (1:100 dilution) just capable of killing in seven days. At the same time some of the specimens of serum were also tested against the same dilution of "Melbourne" virus. The latter strain is more active than B, and a dilution of 1:100 is equivalent to 10 to 100 lethal doses. In Table IV the results are given in the same order of subjects as in Table II. It will be seen that the first three subjects possess no significant antibody; this agrees with the results of the Hirst titrations. In the rest of the series there is no evident correlation with the Hirst antibody level. In contrast with the influenza virus B results, all the first eight subjects possess considerable amounts of neutralizing antibody against influenza virus A ("Melbourne").

Reactions of Subject 1 ("McN.").

We have made a more detailed study of the serum samples from the first subject, on account of the unusual nature of her reactions.

She was given the first intranasal spray (first method) on May 25, 1942, and reported no symptoms whatever. Virus was demonstrated in the nasal fluid, and there was a sharp rise in antibody level (Hirst) from 5 to 150. After an interval of nineteen weeks she was given intranasally a

double spray of virus (third method) on October 5, 1942. There was some nasal irritation the same evening, the symptoms being more severe on the following day. At forty-eight hours, when she returned for nasal washing, she complained of fairly severe headache and muscular aching, and of a sore throat. Her temperature was 99·6° F. Her symptoms cleared up within four days.

In Figure II and Table V, the results of antibody tests on the four serum samples are shown. In each series all four samples were titrated against the same batch of virus. The Hirst titration tests were each done simultaneously; but for the allantoic titrations the work had to be spread over three days.

considerably over sixteen weeks to 45, and the reinoculation resulted in symptomatic infection with a rise of all types of antibody to high levels.

The graph (Figure II) has been drawn with the values for the third sample by all methods arbitrarily taken as equal. It shows clearly the characteristic differences between the three types of antibody titration, a sevenfold rise in Hirst titre corresponding to a 25-fold rise in mice and a 5,000-fold rise in allantoic titre. Absence of antibody can be shown by either mouse or allantoic technique; but with the Hirst test the non-specific inhibitory effect of serum excludes the possibility of very low values.

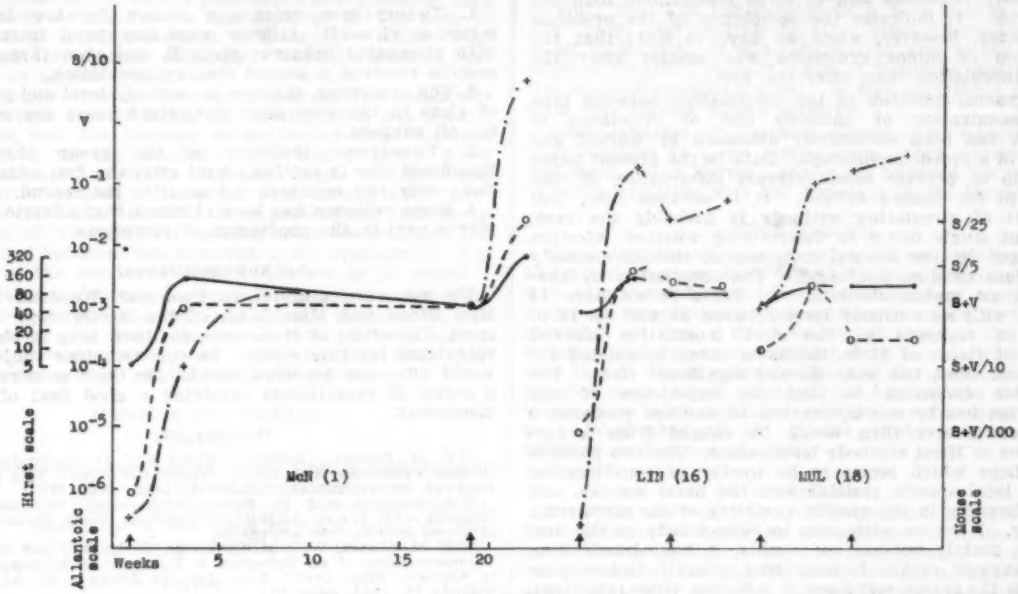


FIGURE II.

Changes in antibody level in three inoculated subjects, "McN.", "Lin." and "Mul.", after two intranasal administrations of influenza virus B. •——• = Hirst hæmagglutination titre; o - - - - o = mouse lung titre; x — · — x = allantoic titre. All scales are logarithmic and equivalent. The relationship between the three scales has been fixed by arbitrarily making the values given by the third sample of "McN." coincide. See text for further explanation. In the graphs for "Lin." and "Mul." the break in the lines corresponds to gaps of 11 and 17 weeks respectively between the first and second inoculations.

TABLE V.

Comparative Serum Titrations of Three Selected Subjects by Hæmagglutination, Allantoic Inoculations and Mouse Intranasal Inoculation Methods.[1]

Number and Subject.	Method.	Successive Serum Samples.			
		1	2	3	4
1. McN.	Hirst.	5	150	45	320
	Allantoic.	1	3	4	7·7
	Mouse.	Nil	S+V	S+V	S/25+V
2. Lin.	Hirst.	40	160	80	80
	Allantoic.	2	6·3	5·3	5·5
	Mouse.	S+V/100	S/4+V	S/3+V	S/2+V
3 Mul.	Hirst.	60	120	120	120
	Allantoic.	4	6	6·3	6·3
	Mouse.	S+V/5	S/2+V	S+V/3	S+V/3

[1] Values for allantoic titrations are the logarithms of the number of 50% infective doses neutralized by undiluted serum. Mouse titration results are shown as the mixtures of serum S and stock B virus V giving an average grade two lesion in the inoculated mice.

The initial serum sample contained no antibody demonstrable by mouse or suballantoic titration, and the value of five for the Hirst titration is not indicative of specific antibody. It is, in fact, a particularly low value for the non-specific inhibition of normal serum. In all probability this subject had had no previous contact whatever with influenza B virus. The first administration resulted in a rise of antibody to a relatively high titre by Hirst test without any appearance of symptoms. The level of antibody shown by mouse and allantoic titration methods, however, remained relatively low. The Hirst titre fell

The point of major interest in this case is the unusual reaction to the second spray of virus with pronounced symptoms and a big rise in antibody level, particularly as judged by *in vivo* methods. The suggestion, already mentioned in discussing Table II, again arises that symptoms following administration of attenuated virus are largely allergic in origin.

Reactions of Two Other Subjects.

On the same graph are shown similar data from two other subjects; "Lin." (16) was chosen as giving a completely normal reaction and "Mul." (18) as being a subject with a relatively high initial antibody level which rose only slightly. It will be seen that both these subjects, who presumably have some basic immunity to influenza virus B, reach a much higher allantoic titration level than "McN." in response to the first administration of virus. This is of particular interest, in view of the evidence obtained by Burnet and Beveridge[4] in regard to the significance of allantoic titres in virus A infections. We have not yet made an adequate investigation of the keeping qualities of this type of antibody, and there are suggestions in the graph that significant falls in value may occur in samples of serum kept in the refrigerator for some months. It seems probable that the apparent rise in antibody level between the second and third samples from "McN." is due to a loss of activity of the second sample, which had been stored for sixteen weeks longer than the third.

DISCUSSION.

These results fully confirm our previous findings that persons with low influenza B antibody level respond regularly to intranasal inoculation with the 40th amniotic passage material "Lee" which we have used in all this work. Similar results in regard to virus B have been obtained by Mawson and Swan,[2] who used the same strain in combination with A type viruses.

The present work gives a more direct indication that the procedure is likely to provide a substantial protection against natural influenza B by showing that a subsequent inoculation produces a much lower proportion of antibody responses and of virus reisolations than the first series. It indicates the complexity of the problems of influenza, however, when we have to state that the proportion of minor symptoms was greater after the second inoculation than after the first.

The general question of the relationship between type and concentration of antibody and of resistance to infection has been extensively discussed by Burnet and Clark[4] in a recent monograph. Data in the present paper may help to provide some relevant information of conditions in the human subject. It is obvious, first, that the level of circulating antibody is probably the most important single factor in determining whether infection (as judged by the normal criterion of rise in antibody level) does or does not occur. The correlation is, however, by no means absolute. In Table II we have 14 subjects with an antibody level between 35 and 80, 12 of whom in response to the first inoculation showed significant rises; of 11 in the same range inoculated for the second time, two only showed significant rises. The reasonable deduction is that the experience of one inoculation has by one mechanism or another produced a resistance greater than would be gauged from a consideration of Hirst antibody levels alone. The two possible mechanisms which seems to be worthy of consideration are (i) local specific resistance in the nasal mucosa, and (ii) differences in the quality (avidity) of the circulating antibody. Here we wish only to refer briefly to the first of these, mainly because our results, as has already been noted, suggest rather forcibly that allergic factors play a part in the symptomatology of influenza virus infections. It is at least interesting that only two of eight persons with very low antibody level should mention any symptoms, while 30 of 38 with antibody should report trivial or definite symptoms. In this laboratory (Beveridge and Burnet[3]) a skin test (intradermal inoculation of heated and diluted allantoic fluid containing virus A or B) has been investigated for possible light that the results may throw on allergy to influenza virus. In children there is a significant correlation between a positive response to the skin test and the presence of the corresponding circulating antibodies; but among adults very few fail to react to skin tests, and a considerable proportion of the reactions are apparently non-specific. Unfortunately the test was not being used until the second stage of the present experiments. All of those tests yielded a reaction to influenza virus B antigen given intradermally. We hope to continue investigation of the part played by these allergic phenomena, and merely record the observations here to draw the attention of workers to an aspect of influenza virus infection that has so far been neglected.

The question of the significance of antibody of different quality in determining resistance to infection will be discussed in another communication (Burnet and Beveridge[6]).

The primary object of this work was to obtain information that might be of value in developing methods of immunizing humans against influenza, particularly against pandemic influenza. The choice of influenza virus B for the investigation was made solely because the immunological phenomena appeared to be simpler than those observed with the more important influenza virus A infections. We consider that the present results provide as definite evidence as can be obtained, short of actual exposure to an epidemic, that the intranasal method is capable of inducing immunity to influenza virus B in a population of young adults. The antibody rises obtained are somewhat better than those reported as following immunization by the subcutaneous method by Hirst *et alii*.[7]

Our results are not directly applicable to influenza virus A or to the hypothetical virus which may give rise to the next influenza pandemic. They do, however, provide a *prima facie* case to justify further human experimentation with living attenuated virus as an immunizing agent against the influenza viruses.

SUMMARY.

1. Twenty-three volunteers chosen for low level of influenza virus B antibody were inoculated intranasally with attenuated influenza virus B, and after three to six months received a second similar inoculation.

2. The symptoms, changes in antibody level and presence of virus in the nose after forty-eight hours are recorded for all subjects.

3. Twenty-one members of the group showed a significant rise in antibody level after the first administration; only two members did so after the second.

4. Some evidence has been obtained that allergic factors play a part in the production of symptoms.

ACKNOWLEDGEMENTS.

We are very grateful to Professor Woodruff and to Miss Stone and Miss Lind, of the Bacteriology Department, University of Melbourne, for their help in obtaining volunteers for this work. To our volunteer subjects we would offer our heartiest thanks for their cooperation in a series of experiments involving a good deal of minor discomfort.

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INTRANASAL VACCINATION OF HUMANS WITH LIVING ATTENUATED INFLUENZA VIRUS STRAINS.

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THE problem of vaccination against influenza assumes considerable importance in view of the possibility that the present war may be followed by a pandemic similar to that of 1918-1919. The subject has been reviewed recently by Burnet;[1] our work has been carried out along lines he suggested and with virus strains he supplied.

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[2] Working with a grant from the National Health and Medical Research Council.

Although there is a tendency for cases of influenza to occur more often among people with a low antibody level against the homologous virus, infection frequently occurs in persons with a high antibody level. Therefore a combination of factors must determine susceptibility to infection. These factors probably include both general and local resistance; the latter term is used to cover various factors not yet fully elucidated, including the presence of virus-inactivating agents in the form of antibody (Francis[2]) or of enzyme-like nature (Burnet, Jackson and Lush[3]) in the nasal secretion, the physiological state of the nasal mucosa at the time of infection, and the existence of local accumulations of histocytic cells or antibody or the two in association. In the hope of augmenting local resistance and at the same time increasing circulating antibodies, we administered the vaccine as an intranasal spray.

This paper records the vaccination of 100 volunteers with a single dose of virus, the ensuing local and general reactions, and the increase in antibodies after fourteen days. The vaccine consisted of pooled allantoic fluids from chicken embryos infected with "W.S." and "Melbourne" strains of influenza virus A and with "Lee" strain of influenza virus B. It is unfortunate that up to the time of writing (five months after vaccination) no epidemic of influenza has occurred in the community. The efficacy of the vaccine, therefore, has yet to be tested.

We also investigated the effect of repeated vaccination on volunteers who showed no antibody response to the first spraying. In some cases vaccines made from earlier amniotic passages were used, with the idea that they might prove a more efficient antibody stimulus.

Materials and Methods.

Volunteers.

The volunteers were drawn from medical and science students, from the scientific and technical staff of the institute, and from personnel of an Australian general hospital. Except for a few cases of mild colds, all the subjects were free from respiratory infection when vaccinated.

Vaccines.

Number I.—For the purposes of comparison with other work, it is necessary to outline briefly the history of the virus strains. "W.S." strain was isolated by Smith and Laidlaw in 1933 and sent to Burnet by Andrewes in 1936. It was maintained in mice until 1940 (approximately 150 passages) with intervals of storage in glycerol in Ringer's solution at -5° C. Since then 100 amniotic passages have been made; we used the 100th.

The "Melbourne" strain, isolated in 1935, was subjected to three ferret passages, and then to approximately 150 to 200 mouse passages. In 1941 amniotic passage was commenced; we used the 50th.

The "Lee" strain of influenza virus B, isolated in 1940, was subjected to several ferret and about 90 mouse passages. Amniotic passage was started in 1941 and we used the 50th.

Each of the three strains was inoculated (0·2 cubic centimetre of 10^{-2} dilution) into the allantoic cavity of four ten-day white leghorn chick embryos. After forty-eight hours' further incubation at 35° C. the allantoic fluid was harvested. Each specimen was tested for sterility by the placing of a loopful on a blood plate, and for activity by the Hirst phenomenon. Only fluid active on 1/100 dilution was used. The four lots of fluid from each virus strain were pooled; the three pools then constituted the "seed" viruses. They were stored in ampoules at -20° C. When vaccine was required a 10^{-3} dilution of each "seed" was inoculated and the fluid was harvested as described above. By using Burnet's technique[4] it was possible to obtain at least eight cubic centimetres of allantoic fluid, free from red cells, from each egg. Equal quantities of the three strains were added, and the mixture was kept at 4° C. until required. The protein content, measured by Mestrezat's diaphanometric method for estimating protein in cerebro-spinal fluid, varied between 30 and 45 milligrammes per 100 cubic centimetres. The infectivity, titrated by suballantoic inoculation in eggs (a method suggested by Burnet[3]), varied between $10^{-7\cdot5}$ and 10^{-9}. No vaccine was used more than fourteen days after preparation.

Number II.—The second vaccine was prepared in an exactly similar manner from earlier amniotic passages of the same three strains—"W.S." from the 47th, "Melbourne" from the 41st, "Lee" from the first or second. The protein content varied from 40 to 60 milligrammes per 100 cubic centimetres and the infectivity titre from $10^{-7\cdot5}$ to $10^{-8\cdot5}$.

Number III.—The third vaccine was prepared from one strain ("Bel.") of influenza virus A by a similar method. The "seed" was "derivative (D)" virus (Burnet[6]), sent to us by Burnet. It was regarded by him as the earliest stage of amniotic passage which it would be justifiable to test as an immunizing agent. It was only three passages from the original human material.

Administration of Vaccines.—Great care was taken to keep vaccines at a low temperature; when necessary, ice was used. Upon Burnet's advice we followed his method[4] of administration, with the omission of the throat spray.

Blood Samples.

Blood samples were taken when the vaccine was given and about fourteen days later. When a second spraying was administered, it followed in about four weeks. To detect an exceptionally slow antibody reaction to the first spraying, we took a third sample of blood at the second spraying and, of course, fourteen days later. After it was seen that in fifteen cases the titres of the second and third samples were almost identical, we omitted the taking of blood on a third occasion. All the specimens of serum were inactivated at 55° C. for thirty minutes when collected, and stored at 4° C.

Hirst Tests.

The Hirst test was employed to measure antibody titres. The technique we used has already been described,[7] and the following simplifications were incorporated. As Hirst[8] has shown that the time between the mixing of the virus with the serum and the addition of the red cells may vary from five to thirty minutes without influencing the end point, we added the red cells at any time between ten and twenty minutes. The red cells were allowed to form a sediment at room temperature, because they did so more quickly than at 4° C.; we found the titre unaltered. By the use of the same concentration of virus (titrated each time against standard antiserum), the serum titres obtained from day to day against any one virus were comparable, and have been recorded in the graphs.

The virus preparations were in the form of infected allantoic fluid, in a dilution just neutralized by a 1/1,000 dilution of the specific antiserum, prepared from the "seed" viruses of vaccine number I.

The two serum samples from each subject were tested together against "Melbourne", "W.S." and "Lee" strains. All the samples were tested twice, and in many instances the results differed upon repetition. If, as happened occasionally, the difference was greater than one tube, a third test was made; the recorded titres were obtained by averaging these results. Original serum dilutions are quoted.

Results.

Results of One Spraying with Vaccine Number I.

The results obtained were as follows.

Antibody Response.—Antibody titres before and after vaccination are recorded in Figures I, II and III. There was a great diversity of results. It is uncertain whether a small increase, such as from 30 to 40, is significant. When it is obtained at two separate tests, and when the same serum dilutions show no increase against the other virus strains, it must indicate some response by the antibody-forming mechanism, especially as small decreases are very rarely observed. However, as most influenza subjects are found to have a fourfold or greater rise in antibody level

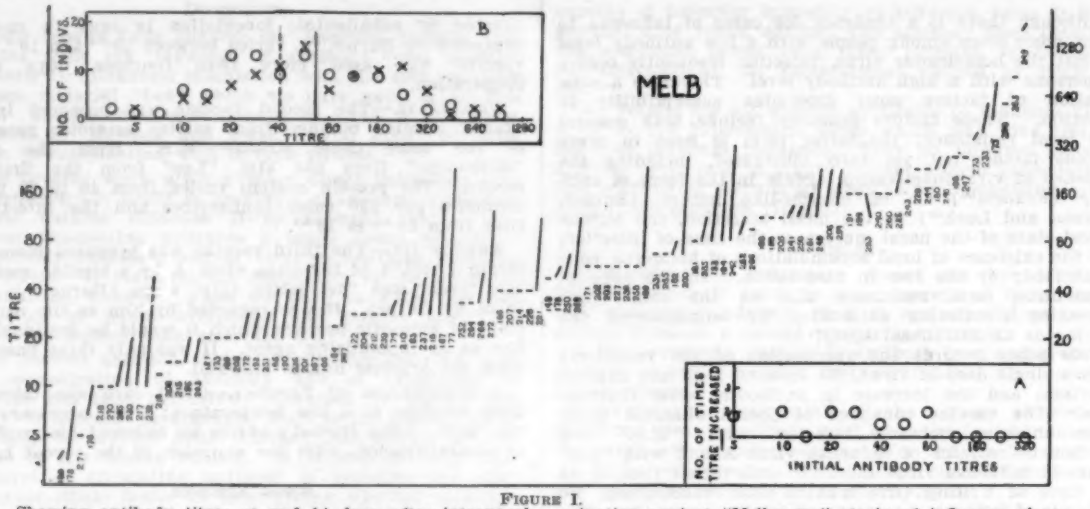


FIGURE I.
Showing antibody titres at and 14 days after intranasal vaccination against "Melbourne" strain of influenza virus. Inset A: average increase of antibody correlated with initial antibody titre. Inset B: distribution of pre-vaccination (o) and post-vaccination (x) antibody titres of 100 volunteers. Average pre-vaccination titre ----; average post-vaccination titre ———.

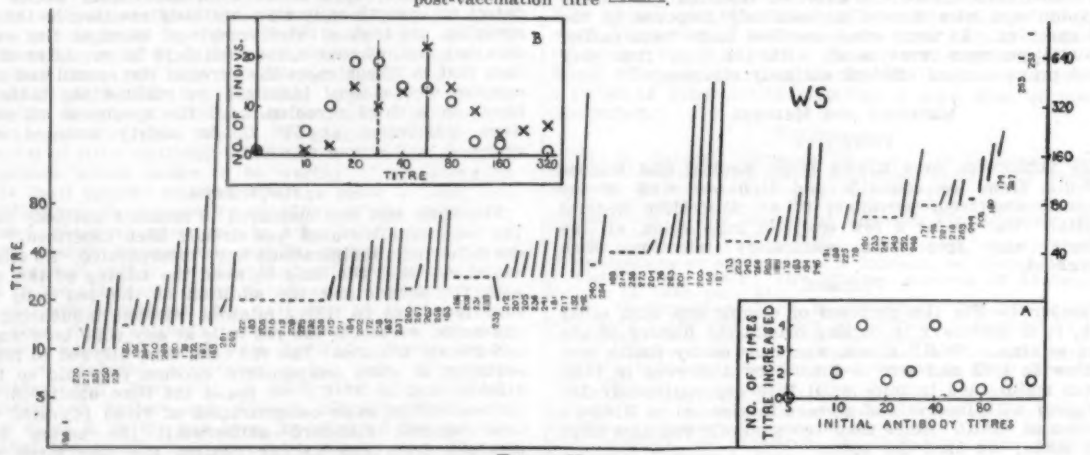


FIGURE II.
Showing antibody titres at and 14 days after intranasal vaccination against "W.S." strain of influenza virus. Inset A: average increase of antibody correlated with initial antibody titre. Inset B: distribution of pre-vaccination (o) and post-vaccination (x) antibody titres of 100 volunteers. Average pre-vaccination titre ----; average post-vaccination titre ———.

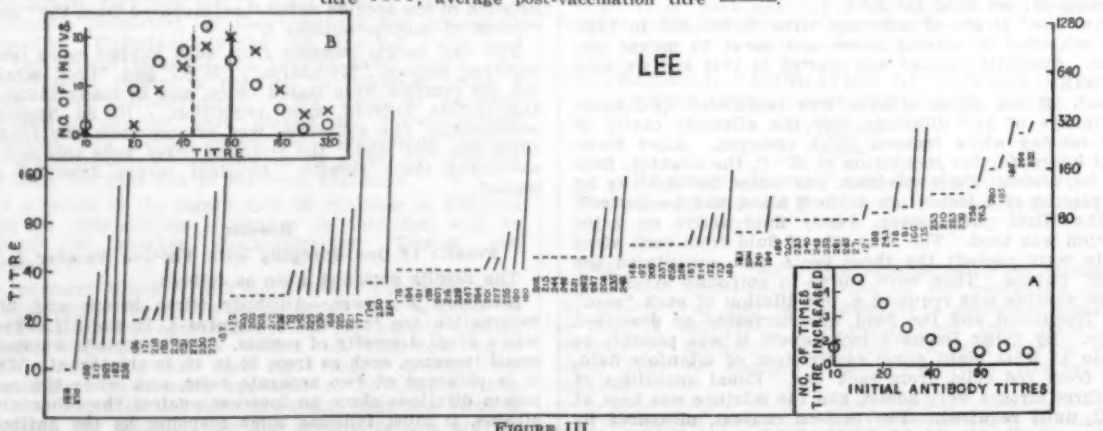


FIGURE III.
Showing antibody titres at and 14 days after intranasal vaccination against "Lee" strain of influenza virus. Inset A: average increase of antibody correlated with initial antibody titre. Inset B: distribution of pre-vaccination (o) and post-vaccination (x) antibody titres of 100 volunteers. Average pre-vaccination titre ----; average post-vaccination titre ———.

during convalescence, we had hoped to evoke at least a twofold increase and have disregarded anything less. The summary of the results in Table I shows that 78% of subjects showed either no increase in antibody or an increase against only one strain. Although some responses far exceeded our expectations (for example, the antibody of Volunteers 259 and 254 against virus B increased ten times and that of Volunteer 169 against "W.S." 26 times), yet the general increase was disappointing. Inset diagrams B in Figures I, II and III show the distribution of antibody titres before and after vaccination. Against "Melbourne" the average level rose from 40 to 75, against "W.S." from 30 to 60, and against influenza virus B from 50 to 80. In the inset diagrams A we have attempted to correlate the average rise in antibody level (none, twofold, threefold *et cetera*) with the initial antibody level. In the case of the two strains of influenza virus A there was no obvious correlation, but with influenza virus B it is noticeable that the greater increases occurred in the lower antibody levels. Burnet[6] obtained the same correlation when he vaccinated 22 people with the "Lee" strain of influenza virus B. We have attempted to correlate symptoms, reported to us up to three days after vaccination, with the degree of increase in antibody and with the initial antibody level. Of 47 subjects showing no rise in antibody level against any of the three strains, only 34 reported no symptoms whatever. Of the 22 developing a twofold or greater increase to at least two strains, eleven had definite reactions, three had slight symptoms lasting less than seventy-two hours, and eight noticed no discomfort. A better correlation exists in the group developing a threefold or greater rise in antibody against at least two strains; of these 14 volunteers, 11 had definite reactions ranging from a "cold in the head" lasting for several days to slight fever and headache. The lack of complete correlation, however, may be due to our difficulty in ascribing correct significance to the clinical reports. There was no correlation between the degree of the clinical reactions and the initial antibody levels against any of the three strains; however, this point was complicated by the presence of more than one virus in the vaccine.

TABLE I.
Summary of Responses of One Hundred Subjects to One Administration of Vaccine Number I.

Number of Subjects.	Strains.		
	"Melbourne."	"W.S."	"Lee."
11	+[1]	+	+
8	+	+	−[1]
2	+	−	+
1	−	+	+
Total 22			
3	+	−	−
14	−	+	−
14	−	−	+
47	−	−	−
Total 78			

[1] "+" denotes a twofold or better rise in antibody level; "−" denotes less than a twofold rise.

Symptomology.—Of the 100 subjects vaccinated, 55 remained free from all symptoms. Twenty of the remainder developed a "feeling as though they were on the verge of getting a cold", characterized by stuffiness of the nose, sneezing and sniffling, and dryness of the throat. Usually these symptoms appeared between six and forty-eight hours after inoculation and had disappeared twenty-four hours later. Twenty developed "colds" of varying degrees of severity; the vast majority were of mild nature. Two had swollen prelaryngeal glands in three to seven days. Only three reported a serious illness. Volunteer 206 suffered from headache and pain in the limbs and chest on the third and fourth days, and on the sixth day had a temperature of 101° F. together with a slight cough. By the eleventh day the symptoms had almost gone. Volunteer 242 had headache and abdominal pain on the seventh day and in the third week had an enlarged spleen and anæmia. Volunteer 241 had a cough and temperature of 103° F. on the ninth day. Neither of the last two illnesses appeared to have any relation to the vaccination, but the first one possibly may have.

Results of Repeated Sprayings with Vaccines Numbers I, II and III.

Forty-seven subjects had no rise in antibody titre against any of the three strains after one dose of vaccine number I. It seems important to know the cause of their failure to respond if large-scale vaccination is to prove successful. It may have been due to any of the following factors: (i) to insufficient virus reaching suitable mucosa owing to temporary nasal blockage; (ii) to an unsuitable condition of the mucous membranes at the time of spraying (it is believed that this factor plays an important role in "catching a cold"); (iii) to the antibody level having already reached its limit; (iv) to the need of a greater stimulus, such as a more virulent virus, for these people; (v) finally, to the possibility that these subjects have a naturally sluggish antibody-forming mechanism.

To make sure that sufficient virus reached the mucosa we repeated the test with vaccine number I on thirteen people, making sure that their nasal passages felt free and delivering four sprays up each nostril. Serum titres are recorded in Table II. Ten subjects showed less than a twofold rise in antibody level to all the strains, and the remaining three showed a rise to only one or two of the strains. Thus the failure of the first spraying to elicit a rise appears to be due to the subject and not to the administration of the virus.

Symptoms following the second spraying were similar to those following the first. We noticed that six out of thirteen subjects (Volunteers 186, 196, 205, 207, 209, 239) showing no response to the first spraying developed mild reactions to the second.

In an attempt to try a more virulent virus we used vaccine number II on seventeen people who did not respond to vaccine number I. However, we have no proof that this vaccine has an increased virulence for man. The serum titres are recorded in Table II. It is significant that in the primary series there were 97 (twofold or better) rises in antibody level out of a possible 300 (32·3%), while in all secondary or later inoculations a total of eight rises in antibody level out of 93 "possibilities" (7·8%) occurred.

Of nineteen people vaccinated, thirteen showed no symptoms. Two hundred and sixty-six had a temperature of 101° F. twelve hours after inoculation; it was associated with shivering, sneezing and nasal discharge, a reddened pharynx and general malaise. The temperature fell to normal within twenty-four hours, but there was still considerable nasal discharge. Two hundred and fifty-six developed hay fever, 176 slight nasal obstruction and 196 a nasal discharge which lasted for two days.

Vaccine number III was used on two people who had been sprayed previously with vaccines numbers I and II. Antibody responses are shown in Table II. This virus is obviously much less attenuated for man than the strains in numbers I or II, but it has not been inoculated into an unvaccinated subject, and so its virulence is not proven. The first volunteer developed symptoms of a mild cold, of forty-eight hours' duration, within twenty-four hours. The second developed stuffiness and itchiness of the nose eight hours after inoculation; within twelve hours he had general malaise, a temperature of 100·4° F., and headache and pain in his limbs which gradually abated in the course of forty-eight hours.

Discussion.

The value of this vaccination can be determined only in the event of an influenza epidemic; in the absence of this test we have no way of estimating the relative importance of increased resistance in the naso-pharyngeal tissues and of circulating antibodies. Thus the rise in antibody levels has had to be used as an index of increased resistance, with the reservation that, if this method of vaccination is used, it may represent only part of the immunity developed.

TABLE II.

Showing Antibody Titres against Various Strains of Virus before Vaccination and after Each Spraying.

Number of Subject.	Pre-vaccination.			Vaccine I.[1]			Vaccine II.			Vaccine III.		
	"Melbourne."	"W.S."	Virus B.	"Melbourne."	"W.S."	Virus B.	"Melbourne."	"W.S."	Virus B.	"Melbourne."	"W.S."	Virus B.
122	30	20	60	30	20	90	30	35	90			
				30	20	90						
171	60	80	20	60	80	25	60	90	40			
				60	80	40						
174	30	160	35	35	240	35	120	800	70	120	800	70
				90	640	35						
176	7	40	40	10	60	40	30	240	80	30	240	80
				15	160	40						
186	40	30	80	40	30	80	40	30	120			
				40	30	80						
196	280	70	20	280	70	20	280	70	20			
				280	70	20						
198	120	60	90	120	60	90						
				120	60	90						
203	60	50	30	60	50	30	60	60	30			
				60	50	30						
205	120	30	30	120	40	30						
				160	60	40						
207	40	30	40	40	40	40						
				40	50	40						
209	20	30	60	20	30	60						
				20	30	60						
238	60	20	30	60	20	30						
				80	40	40						
239	30	30	120	30	20	120	30	25	120			
				30	25	120						
247	280	70	40	280	70	40	280	70	40			
252	35	70	80	35	120	80	35	160	80			
253	900	640	120	900	640	120	900	800	320			
256	120	40	160	140	40	160	140	50	160			
260	160	25	80	160	25	80	160	35	80			
261	120	18	80	160	20	80	160	30	80			
264	35	15	40	35	20	40	50	20	40			
266	100	50	280	100	50	280	100	50	280			
271	5	10	80	5	15	80	7·5	15	140			

[1] In the column under "Vaccine I" the lower figures from subjects 122 to 239 inclusive represent the antibody titres obtained after a second spray of the vaccine concerned.

With one nasal spraying with mixed attenuated influenza virus strains we produced nearly a twofold rise in the general antibody level against each of the three strains. Hirst *et alii*[9] measured the increases in antibody produced by subcutaneous injection of several influenza virus vaccines. When their vaccine number 56 was used, which appears to be of the same class as our vaccines numbers I and II, the mean antibody titre of 150 people was doubled. Thus it appears that, so far as circulating antibodies are concerned, there is little to choose between subcutaneous and intranasal vaccination; by either method the average antibody level can be elevated by about one-eighth the amount of increase seen during convalescence after influenza. This is a disappointingly small increase; nor is the situation improved, except in the case of influenza virus B, by the greater increases occurring in those people with lower initial antibody levels.

Hirst *et alii*[9] were able to produce a sixfold rise in antibody level with their vaccine number 57, wherein infected allantoic fluid was concentrated ten times by centrifugation. The safety of administering such a vaccine by the nasal route has yet to be ascertained. The process of concentration would complicate the large-scale production of a vaccine. The other alternative is the use of more virulent virus strains, and in the search for suitable strains a balance must be reached between virulence and efficiency. Strains such as those comprising our vaccines numbers I and II appear in our hands to be too attenuated, even in the thirteen cases in which we doubled the number of sprays given up each nostril, and in most cases (see Table II) in which repeated sprays were given at intervals of approximately three weeks; we judged the single strain of vaccine number III to be too virulent to use on people not already vaccinated with numbers I and II. It appears to us that strains with degrees of attenuation lying between vaccines numbers II and III merit trial.

There was a slight correlation between the presence of clinical symptoms and the degree of antibody response. This indicates that if a vaccine is to be efficient it will nearly always cause some local and general reactions. Forty-seven *per centum* of volunteers receiving one dose did not respond by an increase in antibody against any of the three strains, despite the fact that not all had high initial antibody levels. Whether or not their local resistance increased, it would be extremely interesting to know why their antibody mechanism did not respond. Repeated spraying with the same or slightly less attenuated strains produced no better reaction in the majority of those tested. Neither of the two who were sprayed with vaccine number III showed a further increase; apparently they were incapable of increasing their antibody titres against "Melbourne" strain. Both of these subjects rarely suffer from colds; but vaccine number III was sufficiently active to invade the mucous membrane of their respiratory tract, which had hitherto proved a very efficient barrier, and produce the symptoms of a "cold" such as they had not experienced for some years.

Another point of interest is the possible effect of atmospheric conditions upon the mucous membranes at the time of spraying—therefore, perhaps, upon the rapidity of spread and penetration by the virus in those tissues and thus upon the success of vaccination. Unfortunately we kept no record of temperature and humidity; the vaccines were administered at atmospheric temperatures probably between 17° C. and 22° C.

There is no doubt that infected allantoic fluid is an exceptionally suitable virus preparation for vaccination. Burnet[1] has listed the advantages, to which we can add the low protein content. Even if, as Hirst *et alii*[9] suggest, a low non-virus protein content of allantoic fluid has no advantage from the point of view of antibody response, it has always been considered preferable to use as pure reagents as are compatible with efficiency.

Burnet[10] has shown that influenza virus B infections have occurred in Australia in recent years; a similar conclusion may be drawn from the number of high pre-vaccination antibody titres against virus B that we found in our series. However, the correlation between the amount of increase and the initial antibody level in the case of influenza virus B, and the lack of it in the cases of "W.S." and "Melbourne" strains, is difficult to understand. It may mean that whereas the majority of people had local nasal resistance against the A strains which distorted the antibody responses, no such resistance hindered the B strain from acting effectively upon the

antibody-forming mechanism. We could find no report of the action of virus inactivating agent on influenza virus B; but as the agent acts upon a wide range of viruses, it is probable that it also affects influenza virus B strains.

Conclusion.

So far as antibody increase is considered, the administration of living, attenuated influenza virus strains by nasal spray appears to have no advantage over subcutaneous injection. However, we consider that there is a possibility that the resultant mild infection of nasal tissues will lead to an increase in local resistance not obtained by subcutaneous injection. This suggestion has yet to stand trial during an epidemic.

Although the average increase in antibody against each of the three strains in the vaccine was approximately two-fold, the individual responses varied from no increase to a twenty-seven-fold increase. Unless all those subjects showing no increase in antibody were already immune, those people would be a source of danger in a community in which large-scale vaccination was relied on in an epidemic. Repeated vaccination failed to raise the antibody levels in the majority of cases. Apparently these subjects need a stronger stimulus—either a greater concentration of attenuated virus or a less attenuated strain. However, it is quite probable that they almost all fall in the 50% to 90% of people who do not contract influenza even in pandemic periods, and that, conversely, the people responding to the nasal vaccine will be just those who will prove susceptible to a respiratory infection like influenza.

Acknowledgements.

We are grateful to Dr. F. M. Burnet and Professor E. Weston Hurst for helpful criticism and advice during the course of this work, and to the former for the provision of virus strains. Our thanks are due also to the commanding officer of the Australian general hospital mentioned and to our many volunteers.

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Reports of Cases.

PULMONARY TUBERCULOSIS: CURATIVE FIBROSIS INDUCED BY INJECTIONS OF TUBERCULIN.

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Case I.

Mrs. M.I.S., aged thirty-one years, consulted me on the reference of Dr. E. R. Roseby on June 4, 1935, and two days later was admitted to the Royal North Shore Hospital of Sydney under my care. Dr. E. R. Roseby had made a definite diagnosis of pulmonary tuberculosis and this was fully confirmed. Mrs. S. had one child nearly seven years old. In 1929 she had been tired and irritable with anorexia and vomiting and catarrh of the nose and throat; she coughed and lost flesh. In 1930 her *appendix caeci* was removed. In 1932 she spent ten months in Thirlmere Hospital and did well, but relapsed on her return home and lost flesh, her weight falling from ten stone seven pounds to eight stone seven pounds. She was thin, pale and sickly, with headache, backache, insomnia, anorexia, flatulence and vomiting. Her chest was long and thin; broncho-vesicular breath sounds and fine râles were heard at and below both apices. Her sputum contained tubercle bacilli. Skiagrams showed tuberculous lesions in both lungs, especially in the apical and subapical regions, in part chronic with cavity formation and in part recent; the gall-bladder was low, but otherwise not affected. The accessory nasal sinuses were clear.

She was kept at rest in the fresh air and given a light diet with extra milk and eggs. Albumose-free tuberculin (T.A.F.) was administered subcutaneously; a first dose of 0·0001 cubic centimetre was given on June 8, and 16 more were given at intervals of three or four days up to 0·05 cubic centimetre on August 10. She had but slight reactions and improved in health. She returned home and had five more injections up to 0·136 cubic centimetre of T.A.F.

Her treatment was then interrupted by a pelvic complication, and in January, 1936, an ovarian cyst was removed. On March 27 she received an injection of 0·001 cubic centimetre of perlsucht tuberculin (P.T.), and 15 more were given up to 0·2 cubic centimetre on June 18; she did only moderately well, as she suffered from further pelvic lesions necessitating diathermy for chronic cervicitis and the removal of a second ovarian cyst about two inches by two inches in size in January, 1937. Thereafter she had more T.A.F. in a dosage of 0·004 cubic centimetre up to 0·16 cubic centimetre, and her condition improved somewhat. Later again she had seventeen more injections of T.A.F., from 0·0035 cubic centimetre on November 10, 1938, to 0·12 cubic centimetre on April 22, 1939. She then appeared restored to health and strength and weighed ten stone seven pounds.

Eighteen months later she suffered an obscure illness, but without recurrence of her tuberculosis. She was for a month in the Royal North Shore Hospital under the kind care of my successor, Dr. C. W. Sinclair, and was submitted to a very complete investigation. She complained of vomiting, pain in the small of the back, headache, cramps, and shortness of breath on exertion. Some dulness to percussion was found in the upper and middle parts of the back of the right side of the chest, and a skiagram showed apical pleural thickening and old bilateral calcified tuberculosis, but no activity. There was slight fever for a few days only after her admission to hospital. Her blood contained 4,900,000 erythrocytes and 7,500 leucocytes per cubic millimetre; the sedimentation rates were 8·5 millimetres on December 17, 1940, and 9·5 millimetres on December 27. There were slight radiographic signs of lumbar spondylitis and of sacro-iliac osteoarthritis, and the amount of gastric chlorhydria was small; but the gastric skiagrams showed normal appearances and there was no occult blood in the fæces. The optic disks, nasal sinuses, gall-bladder, urine, appearances in excretion pyelograms and renal function, all appeared normal.

After massage, applications of hot air and manipulation of the lumbar interspinous joints and of the sacro-iliac joints she was allowed to return home.

In January, 1943, Mrs. S. still had some aches and pains, nausea, anorexia, tremors and insomnia, but she looked well and weighed nine stone ten pounds. Her blood pressure was a little low and there was some broncho-vesicular breathing in the upper part of the right lung. She did not react to 0·03 cubic centimetre of old tuberculin and had no cough or sputum. Her old pulmonary lesions appeared fibrosed or even calcified. Her spinal movements were good and painless and her general health was good.

It would appear that her present maladies are associated with her old pelvic lesions.

Case II.

W.E., a carpenter, aged twenty-eight years, was admitted to my care in the Royal North Shore Hospital of Sydney on February 5, 1933. The diagnosis of pulmonary tuberculosis was indubitable. He had had a bad cold and a cough for two months, and on February 4 and again on February 5 had coughed up half a cup of blood. His sister

had died two years earlier after suffering from pulmonary tuberculosis for seven years. His pulse rate was 128 per minute, his respirations numbered 28 per minute, and his temperature was 101·8° F. The upper part of his right lung lagged in inspiration, and fine crepitations were heard there. Because of the history of recent hæmoptysis I refrained from percussion. His sputum was blood-stained, and in it tubercle bacilli were found. A skiagram showed increased mottling in the upper part of the right lung indicative of a tubercular lesion, and a slight increase in the mottling lower down suggested early spread of infection.

He was kept in bed with ample fresh air, simple nourishing food and extra milk till his fever subsided. Then, when his pulse rate was 98 per minute, his respirations numbered 18 per minute and his temperature was normal, he received injections of albumose-free tuberculin (T.A.F.), an injection of 0·00001 cubic centimetre on February 20, and 20 more in increasing doses at intervals of three or four days (or longer on the occurrence of a reaction) up to 0·0035 cubic centimetre (350 times the first dose) on June 28. His condition improved greatly, but his pulse rate continued to be unduly frequent.

A second skiagram was made on June 6, and the honorary radiographer reported that the condition was more advanced in the right lung and that increase of mottling suggested spread of infection. There was, however, no spread of the disease to be found clinically; the increased opacity of the lungs to X rays was due to a curative fibrosis, such as is described in *The Australasian Medical Gazette* of 1909 at page 309.

W.E. left the hospital on July 8 feeling well and strong, though he still coughed and there was some dulness with bronchial breath sounds in the upper part of the right lung. Despite my warning of the possibility of relapse he considered himself cured, returned to work and had no more treatment.

He did not again present himself till January 7, 1943, when he asked for a certificate of former tuberculosis, as army doctors doubted his statement. He is now stout, ruddy and strong, and weighs twelve stone nine pounds when lightly clad. However, a few clicks may still be heard below the right clavicle and in the right axilla, and his pulse rate at rest is 96 per minute.

Reviews.

THE COMMON FEVERS.

THE editor of *The Lancet* is to be commended for a useful manual on the "Control of the Common Fevers", which has been produced under joint authorship arranged with the help of Dr. Robert Cruickshank.[1]

The book opens with an introductory chapter by Dr. Cruickshank dealing with general principles. As he rightly states, "control of the common fevers is a matter which concerns every doctor and indeed every responsible citizen". In this chapter special reference is made to wartime problems, for example, evacuation and shelter life—the latter having given an extra stimulus to the study of the air-borne infections. Chapters then follow dealing with most of the fevers that are common in the British Isles. Air-borne infections, food infections and some others are included, but why tuberculosis is omitted is not clear.

In a manual written by 21 contributors the standard of the work is naturally uneven. We would particularly recommend the sections dealing with the streptococcal infections. More space might possibly have been given to the non-hæmolytic streptococcal infections, apart from the references to them under puerperal sepsis. The rather dramatic discoveries connected with the hæmolytic streptococci have tended to overshadow their more humble kinsfolk, but of the importance of the latter there is no doubt. The streptococcal chapters summarize important points about the hospital management in such cases, especially in regard to cross-infections with different types of organism, and the growing demand for an adequate number of isolation beds in hospitals is emphasized. "The large undivided ward for the nursing of children with or without infectious disease must be considered obsolete." We agree that a great deal more epidemiological information is necessary before we shall be able to sort out the diseases due to the streptococci, and so place preventive measures on a sure basis.

Welcome stress is laid on the two deadly diseases of childhood, pertussis and measles—diseases which today are more important and have a higher mortality than scarlet fever or diphtheria. The writer is favourable towards prophylactic immunization in pertussis.

Those medical men who have their pet forms of treatment for the prevention of the "common cold" will find them all quietly exploded in the section devoted to this illusive subject.

Apart from smaller points two general criticisms may be offered. First, the book would be very much more useful as a manual (especially to overseas readers) if further chapters could be added. Apart from tuberculosis, which many would like to see included, a tropical disease like malaria is in certain areas a "common fever" of great importance—far greater than many mentioned in the volume. Secondly, we feel that some of the sections do not bear out the title of the book as a manual on control. A great deal of space could be obtained by condensing, and in some cases deleting, material on symptoms, diagnosis, prognosis and treatment—material adequately covered in standard books. These pages could be more profitably used by devoting more space to direct measures of control.

We hope that this volume will have a wide circulation.

[1] "Control of the Common Fevers", by twenty-one contributors, arranged by R. Cruickshank; 1942. London: The Lancet Limited. Demy 8vo, pp. 367, with illustrations. Price: 12s. 6d. net.

PAIN.

"PAIN", by Sir Thomas Lewis, is concerned with mechanism and will appeal to practitioners of physiological outlook.[1]

Lewis is at his best when discussing the interesting work done by himself and his collaborators in the Department of Clinical Research at University College Hospital, much of which is already well known. The investigations on cutaneous hyperalgesia following injuries of the skin and stimulation of nerves, the pain and tenderness of ischæmic muscle and the release of pain-producing substances are dealt with. Also included is the recent work of Lewis and Kellgren upon the pain, tenderness and rigidity following the experimental irritation of muscles, tendons, ligaments and other deep structures.

To explain some of the cutaneous pain reactions, Lewis has for some years postulated the existence of "nocifensor" nerves; and he again describes his views. He omits to mention that in the anatomy department of his own medical school an intensive investigation of cutaneous pain was carried out by the late Professor H. H. Woollard and his colleagues, and that these workers concluded in 1940 that a separate "nocifensor" system of nerves had no existence in fact and that the "nocifensor" reactions were mediated by the ordinary nerve apparatus subserving pain. (Years ago, a similar cleavage of opinion took place at University College Hospital, when the protopathic and epicritic hypothesis of Henry Head was attacked by Wilfred Trotter.)

The sections on alimentary tract pain are not so good, and resolve themselves chiefly into a discussion of conflicting current views, without any finality being reached. There is no attempt to deal with the remarkable clinical peculiarities of ulcer pain, which should form a central theme in a discussion on abdominal pain. Lewis criticizes the theory that the ulcer is itself tender, and holds Hurst responsible for this view, although it was first propounded by Kinsella in this journal in 1928. Hurst, although accepting some of the findings in Kinsella's paper, did not unreservedly accept direct tenderness in the ulcer. He would accept only the visceral serous layer as being possibly tender, and he attributed spontaneous pain to "rise in pressure in the pyloric vestibule". Lewis gives correct references to the literature concerned, in spite of this confusion.

Another confusion of Hurst's views occurs under "Thoracic Contents", where the œsophagus is said to be "sensitive to touch as low as the cricoid".

But the faults are few. Perhaps the oustanding lesson of the book is the demonstration of excellent research work carried out by the simplest methods and with a minimum of apparatus, including a needle, a hypodermic syringe, a watch, a sphygmomanometer and such like. The chief instrument is careful clinical observations coordinated by a keen mind.

[1] "Pain", by Thomas Lewis, M.D., F.R.S.; 1942. New York: The Macmillan Company. 9¼" x 6¼", pp. 208, with illustrations. Price: 12s. 6d. net.

The Medical Journal of Australia

SATURDAY, MAY 1, 1943.

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THE SCIENTIFIC EXPERT AND COMMON SENSE.

ANY smugness or conceit that might exist among medical men in Great Britain received a sharp rebuke when, as reported by "Observer" in *The Australian Quarterly* for September, 1942, Mr. Bevin, Minister for Labour, during a discussion on the problem of fatigue in munition factories, promised to have inquiries made about the signs of fatigue among juvenile workers in cotton mills. Mr. Bevin was asked two questions. The first was: "Through what agency is the right honourable gentleman making these inquiries?" The reply was: "Through the factory inspectors." The second question was: "Will this include expert medical advice?" To this Mr. Bevin made reply: "We do not rely too much upon experts, we have to apply some common sense." Nothing could be more direct and unambiguous than this statement. Among certain persons it may arouse resentment, that the wisdom of a learned profession should be impugned; others may feel amusement or even pity for the person who made it, attributing to him either lack of understanding or prejudice. Seeing, however, that this forthright remark has come from a man of Mr. Bevin's intelligence and ability, the wisest course for medical men and women to adopt is to inquire what qualifications are needed by an expert, whether they have the qualities that would justify their assumption of the role, and whether, appearing as experts, they have through want of care or for any other reason done anything that would justify a general condemnation.

Experts have arisen because in the evolution of the human race life has become more and more complex. Whereas man once had little to worry about apart from the provision of food for himself and his dependants and their protection from marauders, he is nowadays very much a creature of circumstance, struggling for existence in a world made complex by the advance of science, hedged round by social conventions and political obscurities of his own creation and groping almost blindly in a maze of economic entanglement that has grown up around him. This is known as modern civilization. It is all very difficult. Man quite naturally wishes to make his position in society as secure as possible; he wants to control his circumstances rather than allow them to control him. It matters not whether he seeks control as an individual or as a member of a group, power will be denied him unless he has knowledge and understanding, and these can be acquired in the world of experience either by search and application or by taking knocks as they come in the rough and tumble of life and treating them as so much profit or loss. For a great deal of the information on which opinions are based and plans for action laid he relies on authority—the authority of those who by common consent are credited with knowledge and possibly wisdom. And incidentally it may be remarked that most men, especially if they have had a scientific training, would fain be numbered among those who are said to enjoy authority—an understandable, if not always laudable, ambition. Since knowledge and understanding may be acquired in the world of experience, we may recall that experience has in fact been described as the mother of knowledge. It has also been called the teacher of fools. The point is that to become an expert a man needs to have some natural intelligence; the title of expert is not for the fool, be he ever so battered in the sea of experience. Experience was said by Oscar Wilde to be the name that men gave to their mistakes. If this is so we may remember that in the terms of the Latin saying "*experientia docet*" man may profit from his mistakes if he will. If he does turn them to a useful purpose, he may then be inclined to agree with Oscar Wilde in his further contention that the only things one never regrets are one's mistakes.

So far our discussion has shown the expert to be, in the words of the "Concise Oxford Dictionary", one whose special knowledge causes him to be regarded as an authority. If his knowledge is to be of any use he must be able to apply it, especially when he is asked to do so by those not learned in the subject with which he deals. The scientist is always faced with the danger of suffering from a warped mental outlook. When the scientifically trained man is a medical graduate who deals with science applied to the human individual the danger of distorted vision becomes greater. The *post hoc* easily becomes the *propter hoc* and without any realization of error general conclusions are drawn with no justification from particular instances. The single-minded focal sepsis "expert" provides a constant example of this unfortunate event, being so wedded to his ideas that in the words of one of our medical wags he almost lives with "the old focus at home". It does not take a man of Mr. Bevin's insight to appreciate the futility of the one-eyed expert on his hobby horse. From this kind of man common sense is demanded. But what is common sense? To this nine persons out of ten will reply: "It's just common sense." Turning to the "Concise Oxford Dictionary" again, we find common sense described as "good practical sense in every day affairs". In the "Encyclopædia Britannica" common sense is stated to signify usually the intelligence of normal people as distinguished from the views more or less peculiar to those who belong to special schools of thought. "The contrast intended is sometimes between the views of average people as against the views of peculiar or exceptional people, and sometimes that between the attitude of those who have just a general education and the attitude or outlook of those who have specialized in some way or other." If our expert then is to use common sense he must enlarge his outlook and try to see things as "normal", ordinary or average people see them. But common sense

alone will not be sufficient; were it sufficient, the untrained man could give an opinion just as valuable as the scientist's. The scientist, becoming a common-sense person, will need to apply his knowledge without bias and with keen critical judgement. Common sense is often almost intuitive; in matters scientific intuition, if it has a place, must be combined with critical judgement.

From this discussion on the qualifications needed by an expert it is clear that the possession of a degree or diploma in medicine does not in itself entitle the holder to claim the authority of an expert. Unfortunately there is no one who shall determine which graduates shall and which shall not be regarded as qualified to give what are known as expert opinions. The determination is left to each individual. Unfortunately also some would-be experts are good talkers and know how to bring themselves to the public notice. Further, no one can rightly claim that the daily Press is always restrained in its use of headlines to report the views of experts nor careful to give the opinions in their proper context. Whether common sense and critical judgement can be deliberately acquired by those who lack them, may be open to argument. It is quite certain, however, that there are specially trained persons who have set out to temper their specialized knowledge with experience of the world at large and its ways, and have attained rank that may be described as that of the common-sense expert. There come to mind a man of science who worked during vacations among transport workers that he might understand his brother man, a professional man who after a term at Oxford as a Rhodes Scholar returned to Australia as an able bodied seaman with the same object, and a professional woman who worked in factories and in domestic service that she might extend her outlook. Such drastic steps as these will seldom be possible; the main thing is to recognize that the horizon needs widening. Once this has happened it should not be difficult for the person concerned to set about the devising of means. The ultimate goal should be freedom of a specialty and citizenship of the universe. If this goal was sought earnestly by those setting themselves up as experts and if the giving of expert opinions could be confined to such persons, it would be impossible for Mr. Bevin or anyone else to call in question the value of expert advice.

Current Comment.

DIPHTHERIA OF THE SKIN.

DIPHTHERIA of the skin is not such a rare condition as some people seem to think. It is as a rule described shortly in text-books on dermatology, but at least one important text-book makes no mention of it. When the condition is mentioned, it is generally dismissed in a few short paragraphs. During the progress of war, skin diphtheria becomes more important because wounds may become infected by Klebs-Löffler bacillus, and from other chronic skin lesions the organism is sometimes recovered. In a book published in 1923 by the Medical Research Council of the Privy Council on the bacteriology, pathology and immunology of diphtheria, we read that in Germany during the war of 1914-1918 a condition known as wound diphtheria was common, but it was not clear whether infection of the wounds was due to *Corynebacterium diphtheriæ* or to some harmless diphtheroids. Though extensive infection of wounds with *Corynebacterium diphtheriæ* was not observed in Great Britain during the war, some reports of such an occurrence were published. In many instances the infection was due to a diphtheroid organism. It is stated that when infection of a wound by a virulent bacillus is proved to have taken place, it often gives rise to no obviously harmful results either locally or generally. At the same time, certain observers expressed the opinion that in all cases an improvement was effected by the use of antitoxin. In view of the fact that most recorded cases had occurred in adults, many of whom might be assumed to have been immune, toxic symptoms were expected to be absent. Writing in *The Lancet* of September 13, 1919, Colin McK. Craig described observations made on the desert or septic sore amongst European troops and its association with faucial diphtheria. He found that this septic sore was a distinct clinical entity and had a geographical distribution. The ætiological factor in his opinion was the Klebs-Löffler bacillus and this was responsible for the specific character of the lesion. He also held that this organism possessed a low virulence and produced constitutional disturbances only in specially susceptible persons, and he believed that under favourable conditions the sores might be responsible for outbreaks of faucial diphtheria. Craig refers to investigations made by C. J. Martin in Australian units. Martin examined hairs extracted from the vicinity of a septic skin lesion and found diphtheroid organisms. Later on he investigated one strain more thoroughly and found that it gave reactions typical of the Klebs-Löffler bacillus. This infection was not associated with obvious constitutional disturbance, and Martin concluded that the diphtheroid infection was superimposed upon some pyogenic coccal lesion. Craig suggested that the failure of other observers, such as Crowe (*The Lancet*, Volume II, 1918, page 667), to isolate the Klebs-Löffler bacillus was due to the fact that the investigations were made in base hospitals where the lesions were more chronic and pyogenic organisms therefore more numerous.

A recent communication on cutaneous diphtheria comes from J. B. S. Cameron and E. G. Muir, who have been working in Northern Palestine.[1] From September to December, 1940, they observed 66 cases of cutaneous diphtheria. During this same period other types of diphtheria were developing in the same unit. Thus there were 26 cases of nasal diphtheria, 79 cases of faucial diphtheria, 66 cases of cutaneous diphtheria, and 78 carriers. Swabbings were made from the nose and throat of all patients with cutaneous diphtheria. Of the 66 cases, 42 were unassociated with positive findings indicating the presence of diphtheria elsewhere in the body. Of the remaining 24 patients with cutaneous diphtheria, eight had faucial diphtheria, four had nasal diphtheria, and three had both nasal and faucial diphtheria; there were ten carriers. The infection manifested itself in the skin in two forms, acute and chronic. The acute form was always associated with a positive lesion of the throat, or, more commonly, the nose. The chronic form was invariably superimposed on a skin lesion which might be any form of skin disease. The commonest associated condition was the desert sore, but others were scratches, insect bites, impetigo, scabies, staphylococcal folliculitis and epidermophyton; one case occurred with typical *herpes zoster*. The acute lesion was found both on unbroken skin and at the site of previous trauma. Direct transference through nose-wiping was responsible for certain of the lesions found on the unabraded skin of the radial aspect of the forearm and dorsum of the hand. One patient had a mosquito bite on the right upper eyelid. This broke down and became infected by diphtheria organisms. Faucial and nasal diphtheria and diphtheritic conjunctivitis were also present. The patient later developed polyneuritis. The chronic sores were almost invariably multiple and were usually found on elbows, forearms and backs of hands, knees, legs and ankles. The chronic sore was usually circular or oval. It was punched out and clear-cut, and varied in width from one-third of an inch to as much as two inches. The edges were hard, raised and rolled. The base of the ulcer was flat and even; sometimes it was covered with a leather-like dark scab membrane beneath

[1] *The Lancet* December 19, 1942.

which lay unhealthy looking pus. Cameron and Muir point out that acute and chronic sores may be encountered in the same patient, and that in these circumstances the acute lesion is usually a contact infection of healthy skin from the chronic lesion. The diagnosis can be proved only by the discovery of the *Corynebacterium diphtheriæ* and by the establishment of its virulence. In the series reported no diagnosis of diphtheritic infection was made without bacteriological verification. In a larger number of cases a staphylococcal lesion provided a basis for the diphtheritic sore. In nearly all these cases *Staphylococcus aureus* of similar type to that present in the skin infection was found in the nose. Cameron and Muir think that this is in favour of the suggestion that a large number of skin infections with staphylococci are of nasal origin, and that in such cases a staphylococcal vaccine may be of therapeutic value. The diphtheritic infection was thought to have originated in the native population. The acute sores always healed rapidly, but the chronic sores were very indolent and usually took several weeks to heal. Diphtheritic paralysis occurred in 12 of the 66 cases, and in five of these no focus of diphtheria other than that present on the skin could be found. Cameron and Muir point out that others have made a similar kind of observation.

The question of treatment remains to be considered. Apparently the acute lesion calls for little treatment other than that of the faucial or nasal diphtheria, a bland moist dressing being all that is required. With the chronic lesion treatment is more difficult. Prevention will first demand attention. As already stated, Cameron and Muir regard the native population as responsible. They exonerate the horse as a source of infection, all their investigations in this regard having yielded no positive evidence; other observers have blamed the horse. In spite of their exoneration of the horse, they include "the increased tendency to abrasions in certain occupations such as grooming" among the factors that may play a part in infection. The other factors mentioned by them are climate, excessive exposure to the sun, the lack of fresh fruit at certain seasons, the difficulty of keeping scratches and bites covered, clean and moist, and the attacks of insects. This raises the question whether the view advanced by Craig is correct in regard to the condition of desert or septic sore. Maybe it is, but that would not exclude the possibility of the contamination of a wound or other sore by the Klebs-Löffler bacillus. In regard to actual treatment diphtheria antitoxin will be given, as Cameron and Muir gave it, in all cases. They raise the question as to whether the incidence of paralysis does not justify the giving of large doses. They had no specially notable results with sulphonamides; even when these drugs were applied locally, they did not seem to be more effective than other methods of treatment. Dressings that did not stick gave the best results. They insist that it is unwise to adopt only one method of treatment—whatever is done, any large diphtheritic sore is likely to take three or four weeks to heal.

MORPHOLOGY OF THE ERYTHROCYTES IN ERYTHROBLASTOSIS FŒTALIS.

MUCH has been written lately about *erythroblastosis fœtalis* and its relationship to the Rh factor. Levine and his associates have shown that about 90% of infants with erythroblastosis have in their red blood cells an agglutinogen designated as Rh which the mother's blood lacks. The demonstration of anti-Rh agglutinins in the serum of a large percentage of the mothers of these infants favours the hypothesis that *erythroblastosis fœtalis* is the result of an intrauterine antigen-antibody reaction. Darrow had previously advanced this hypothesis on purely theoretical grounds, but with no knowledge of the antibodies concerned. It will be remembered that acute hæmolytic anæmias due to auto-antibody reactions have been observed in human beings and induced experimentally in animals. Examination of the blood of these animals has shown fairly consistent blood changes. During the initial phase of hæmolysis, the mean cell diameter decreases and the mean cell volume increases, the cells assuming a spheroid shape. After several days the mean diameter rises above normal with the simultaneous appearance of macrocytes, nucleated red cells and increased numbers of reticulocytes. At this time the Price-Jones curve is frequently biphasic and Dameshek has stressed this point as being of diagnostic importance in such anæmias. If, therefore, it can be shown that changes similar to these occur in the blood in *erythroblastosis fœtalis*, we have some additional evidence in support of Levine's hypothesis.

Reasoning thus, E. H. Reisner embarked on a study of histories and blood films from twenty-four infants with *erythroblastosis fœtalis*.[1] Of these, twelve were classified as manifesting *hydrops fœtalis* and twelve *icterus gravis*. The basis of this classification is of interest. For the sake of consistency, all patients who showed even a small amount of œdema were classified as having *hydrops fœtalis*. Of twelve infants so classified, five were stillborn, four died shortly after birth and three survived. At one time the term *hydrops fœtalis* was used only for infants with massive anasarca; it is a step in the right direction to extend its use to infants with slight or moderate œdema, as it emphasizes the importance of recognizing the less obvious cases of *erythroblastosis fœtalis*. As controls, Reisner examined blood films from five normal newborn infants and from twelve infants suffering from intracranial hæmorrhage, *asphyxia neonatorum*, pyloric stenosis, pylorospasm, infection and obstructive jaundice. Some of these infants were profoundly anæmic. Price-Jones curves were made by the direct measurement with an ocular micrometer scale of the diameters of three hundred consecutive round cells in dried smears. In 23 of 24 cases of *erythroblastosis fœtalis* the Price-Jones curves were biphasic with macrocytic peaks and in one case definite microcytosis was present. Roughly speaking, a biphasic Price-Jones curve indicates that anisocytosis is present, and is of such a kind that cells somewhat smaller than and cells somewhat larger than the average outnumber cells of average size. There is, as it were, a hiatus in the gradation of cell size. Price-Jones curves plotted from blood of normal infants and twelve infants with various diseases were in no instance biphasic, although several of the films showed pronounced anisocytosis. Reisner concludes that the morphological changes in erythrocytes in *erythroblastosis fœtalis* resemble, in some respects, those observed in experimental hæmolytic anæmias due to antigen-antibody reactions. He observes that we must bear in mind that the final word has not yet been said on the subject of the Rh factor; his work, however, supports the hypothesis that an antigen-antibody reaction of some kind is the cause of *erythroblastosis fœtalis*.

Examination of blood smears in six of Reisner's cases of severe *erythroblastosis fœtalis* revealed varying numbers of megaloblasts. It is, of course, well known that megaloblasts are found in the blood in this disease. Reisner suggests that the presence of megaloblasts and macrocytes may be, in part at least, the result of a deficiency of the erythrocyte maturation factor. This in turn is due to liver damage. Varying degrees of extramedullary hæmopoiesis are observed in the liver in *erythroblastosis fœtalis*, and in severe cases there is usually extensive necrosis of the hepatic parenchyma.

These observations imply that treatment with liver extract may be of use in erythroblastosis. Too much, however, cannot be expected from it. According to most observers, the macrocytic anæmias of hepatic disease do not respond well to injections of liver extract. Several workers have administered large amounts of liver during pregnancy to patients who have previously borne infants with erythroblastosis. In a few cases, good results seemed to follow: in others no effect whatever was observed. Still, in the present state of our knowledge, it is worth while trying any form of treatment that may possibly benefit the victims of this tragic familial disease.

[1] *Archives of Internal Medicine*, February, 1943.

Abstracts from Medical Literature.

MEDICINE.

Essential Hypertension.

STUDIES of patients exhibiting "essential" arterial hypertension have suggested that there may be a variety of contributory factors to its onset and that it is not a single disease. H. A. Schroeder (*The American Journal of the Medical Sciences*, July, 1942) has investigated a series of 50 cases in which the date of onset of the elevated blood pressure was known. Detailed examination of possible ætiological factors was made, and in addition to full physical examination there were carried out in each instance a cursory psychological examination and studies of the genito-urinary tract, particularly relating to renal function, obstruction and infection; basal metabolic rates were estimated and X-ray examinations of skull and larger arteries were made. All patients had a systolic pressure of 150 millimetres of mercury on at least three occasions, but the pressure usually was between 140 and 150 millimetres and the diastolic pressure was more than 85 millimetres of mercury, usually less than 100 millimetres. Two factors were suggested as being necessary for the occurrence of essential hypertension, firstly a constitutional one and secondly a morphological one. In relation to the constitutional factor, there were 39 patients who gave a family history of hypertension; emotional instability occurred in 44 cases; flushing with excitement, excessive perspiration, cold extremities, tendency to worry and irritability were other factors commonly present. These symptoms usually antedated the onset of hypertension, sometimes becoming more prominent as the blood pressure rose. With reference to the morphological factor, renal diseases of various sorts were found in 37 cases. Relatively severe renal disease as estimated anatomically was associated with very little nervous instability; slight renal disease and more pronounced nervous disturbance have been found together. There was no relation between the severity of the renal lesion and the height of blood pressure. In a few cases a precipitating factor could be determined, emotional causes or renal infection. It can be concluded therefore that arterial hypertension results from several factors, one or more of which may be dominant in different individuals.

Treatment of Pernicious Anæmia.

M. R. STRAUSS, A. J. POTEK, JUNIOR, F. J. POHLE, H. J. FOX AND J. H. BURCHNAL (*The New England Journal of Medicine*, June 25, 1942) report the study of 80 patients suffering from pernicious anæmia, treatment in each case ranging from five to nine years. Individual maintenance requirements for liver extract vary widely, and the determination of the requirement is a difficult task often necessitating years of observation. One of the criteria of adequate treatment is the maintenance of normal red cell values, but this is often difficult to apply in actual practice. One reason is the wide variation of normal red cell counts in healthy individuals: some rare individuals may have a normal red cell count of less than 4,000,000 per cubic millimetre. Another difficulty, only recently appreciated, is the fact that a single red cell count performed with satisfactory technique in the usual manner at an approximate level of 5,000,000, is significant only within a range of 1,600,000. In fact, a difference of over 1,000,000 may be expected to occur once in every twenty pairs of consecutive red cell counts. The performance of duplicate determinations on each observation only increases the range of significance to 1,100,000: the mean of 20 counts is significant within a range of 340,000, but this is hardly a practical procedure. Estimation of the mean corpuscular volume appears to be subject to even wider variation, whilst the plotting of Price-Jones curves, the most accurate determination of red cell normality, is too laborious for routine use. The authors state that, apart from a red cell count persistently under 4,000,000 per cubic millimetre, adequacy of treatment is determined purely by clinical means and subjective symptoms.

Liver Therapy in Pernicious Anæmia.

B. L. DELLA VIDA (*The Lancet*, September 5, 1942) states that the reticulocyte response does not give an accurate indication of the effectiveness of liver treatment in pernicious anæmia and is therefore not reliable by itself as a means of assessing the potency of liver extracts. He claims that the formula $I = 0{\cdot}93 - 0{\cdot}214E_0$ (where I is the average weekly increase in red cells during the first two weeks of treatment and E_0 is the red cell count before treatment) has been found to express a satisfactory response to treatment and proposes it as the standard equation for the assessment of the potency of liver extracts.

S. C. DYKE (*ibidem*) points out that the United States Pharmacopœia has laid down that wording on labels of or in package literature accompanying liver extract must state the daily dosage necessary to produce a "satisfactory hæmopoietic response" in a case of pernicious anæmia. He states that it is unsafe to use the reticulocyte response as a criterion of satisfactory hæmopoietic response as suggested by the pharmacopœia and that the increase of the red cells can alone be regarded as a true criterion.

The Chemical Aspects of Cancer.

C. P. RHOADS (*Journal of the Mount Sinai Hospital*, May-June, 1942) discusses the carcinogenic chemicals, and notes that 140 years elapsed before Percival Pott's observations on chimney sweepers' careers were extended by the application of the experimental method. Dibenzanthracene, given orally to animals, is excreted as dihydroxydibenzanthracene, which, the author suggests, is a protective conversion. Also the liver cancer produced almost invariably in rats fed on a diet of brown rice, carrot and butter yellow did not occur in controls which had either 15% yeast or 5% liver extract powder (Lilly 343) added to the diet. Further experiment established the protective acetylation of the metabolite of butter yellow which poisons Coenzyme I, and also that, under certain conditions, the cancer tissue is immune to the metabolite which damages the normal cell and so presumably produces the cancer. Possibly a compound capable of reversing this last phenomenon may yet be found.

Gastroscopic Observations in Pulmonary Tuberculosis.

THE presence of gastric symptoms in patients with advanced pulmonary tuberculosis and the absence of any recognized gastric lesions in this disease led J. Flexner and O. Baum (*The American Journal of the Medical Sciences*, July, 1942) to examine with a gastroscope a series of 27 patients who had suffered from pulmonary tuberculosis for a number of years. They set out to answer three questions: First, can a specific lesion be demonstrated in the stomach in late stages of pulmonary tuberculosis if the gastric mucosa is examined through the gastroscope? Second, what effect has the prolonged swallowing of purulent material on the gastric mucosa? Third, can the gastroscopic findings be correlated with the presence or absence of digestive complaints? No specific lesion was found, even though five patients had tuberculous enteritis. Chronic superficial gastritis was found alone and combined with chronic atrophic gastritis in an unusually large number of patients. The abnormalities of the gastric mucosa, however, could not be correlated with the duration, severity or type of tuberculosis, nor with the quantity of sputum expectorated. Gastric symptomatology failed to follow directly the gastroscopically demonstrated lesions; but this was thought to be influenced by bed rest, the reduction in food consumption caused by anorexia, and frequent absence of free hydrochloric acid in the fasting specimen.

Renal Glycosuria.

MEYER FRIEDMAN *et alii* (*The American Journal of the Medical Sciences*, July, 1942) have undertaken a study of simultaneous measurements of the glomerular filtration rate, the renal blood flow, the filtration fraction and the tubular reabsorption of glucose at different plasma concentrations of glucose in five patients with moderate renal glycosuria and in seven controls. Those in the control groups had normal blood pressure and no signs or symptoms of kidney disease. The urine of each contained no detectable glucose when tested by the Benedict test before and two hours after the ingestion of 100 grammes of glucose. The fasting plasma sugar content of each was also within normal limits. Each of the five patients had a glycosuria without hyperglycæmia. There was no progression in the glycosuria during a period of observation of several years. The results show that the effective renal blood flow, the glomerular filtration and the filtration fraction are within normal limits in the individual with moderate renal glycosuria. The observations also indicate that, whereas tubular reabsorption of glucose in the glycosuric patient is less than that found in the non-glycosuric individual at moderate plasma concentrations of glucose (100 to 200 milligrammes per 100 cubic centimetres), this comparative diminution in reabsorption in the glycosuric subject disappears at higher plasma concentrations of glucose; in fact, it is suggested that the renal glycosuric absorbs glucose from the tubular fluid

more readily than the non-glycosuric individual. These facts are strong evidence against this condition being associated with a serious organic or physiological derangement of the kidney.

Subacute Bacterial Endarteritis Complicating Patent Ductus Arteriosus.

A. S. W. TOUROFF (*The Journal of Thoracic Surgery*, October, 1942) reports the cases of six patients suffering from subacute endarteritis due to *Streptococcus viridans* complicating patent *ductus arteriosus*, all of whom were cured by operation, namely, ligature or division of the duct. It is stated that the operation is likely to be attended by a low mortality and a high probability of cure if carried out in the early stages of infection.

Nicotinic Acid in Angina Pectoris.

F. J. NEUWAHL (*The Lancet*, October 10, 1942) has given intravenous infusions of 100 to 300 milligrammes of nicotinic acid in 0·05% solution in normal saline solution to six persons suffering from angina of effort. The infusions were given about twice a week for about three weeks. Subjective and objective evidence of continued improvement followed and this was maintained over a period of six months. The action of nicotinic acid on blood pressure and heart rate was constant in almost every case, both being reduced.

Peptic Ulcer and Irritable Colon in the Army.

D. T. CHAMBERLAIN (*The American Journal of Digestive Diseases*, August, 1942) discusses the incidence of peptic ulcer and irritable colon among patients admitted to the gastro-intestinal section of a general military hospital; the patients totalled 316 out of 1,755 medical cases, being 9% of the total admissions and 18% of those admitted to the medical service. Functional digestive disease accounted for 113 cases, whilst 98 patients had peptic ulcers, gastric ulcers being only three of these. Patients suffering from peptic ulcer had averaged five and a half months of military service before the symptoms became severe enough to require admission of the patient to hospital. The chance that a man with peptic ulcer may escape disabling symptoms in the service is slight, and he is unfit for military service. The large group with functional digestive disease presents a difficult problem, as it is not possible to eliminate many from this group at the beginning of their service. They have to be observed, and the true status of each patient evaluated in relation to the military service. True psychotics, the constitutionally inadequate and the morons must be weeded out and discharged, whilst the remainder must be returned to duty whenever possible.

Hypertensinase.

L. DEXTER (*Annals of Internal Medicine*, September, 1942) describes investigations into the hypertensinase content of plasma of normal hypertensive and nephrectomized dogs. The pressor substance hypertensin was demonstrated in the renal venous blood of ischæmic kidneys and was shown to be identical with the pressor substance produced by the *in vitro* incubation of renin with blood globulins. Hypertensin is said to be the cause of hypertension due to renal ischæmia. Others have described a substance hypertensinase which destroys or inactivates hypertensin. The unit of hypertensinase is defined as the amount which in a volume of 10 cubic centimetres destroys 0·5 unit of hypertensin in four hours at a temperature of 37° C. It was found on investigation that the hypertensinase content of plasma of dogs from whom the kidneys had been removed forty-eight hours previously and of dogs rendered hypertensive by renal ischæmia was normal.

Renin.

B. A. HANSSAY, E. BRAUN-MENENDEZ AND L. DEXTER (*Annals of Internal Medicine*, September, 1942) discuss the destruction and elimination of renin in dogs. Renin, a pressor substance when injected intravenously, was described by Tigerstedt and Bergmann in 1898. Renin plays an important role in the development of experimental hypertension. Hypertensin or angiotoxin is a pressor and vaso-constrictor substance present in the venous blood of ischæmic kidneys, and can be obtained *in vitro* by incubation of renin with blood globulins. Renal ischæmia determines the secretion of renin, which acts on blood globulin and gives rise to hypertension which produces vaso-constriction. The authors showed that two to three cubic centimetres of renin injected intravenously into dogs disappeared from the blood in thirty minutes. In dogs from which the kidneys had been recently removed the disappearance took one to three hours. Only a fraction of renin injected was found in the urine, but no substance was found in the blood which caused disappearance of renin from the blood. In uræmic dogs renin disappeared slowly from the blood; apparently its disappearance was due to destructive action of the tissues. The mechanism of this destruction could not be demonstrated.

Syphilitic Aortitis.

WILLIAM H. GORDON, FREDERIC PARKER, JUNIOR AND SONIA WEISS (*Archives of Internal Medicine*, September, 1942) publish a detailed report of three cases of gummatous aortitis, and discuss the result of an analysis of 360 cases of syphilitic aortitis. They report that from their own experience and from a review of the literature, it is concluded that true macroscopic gummatous aortitis is rare, and that the number recorded up to date including the three they have reported does not exceed ten. Gummatous aortitis is mainly localized in the media, but usually the intima and the adventitia are also affected. Gummatous lesions of the aorta are responsible for symptoms only if they result in narrowing or occlusion of the coronary arteries, or in perforation of the aorta. Dyspnœa, orthopnœa, precordial distress, cardiac asthma, pulmonary œdema and hæmoptysis, when present, are referable to such lesions of the coronary arteries or the aorta. Of the 360 cases of chronic syphilitic aortitis studied by the authors, microscopic gummata occurred in eight (one in forty-five), but they state that this ratio is minimal, and that possibly in all cases of chronic aortitis the lesions go through a stage of microscopic gummatous aortitis. It was found from this study that atheromatous changes over the area affected by the syphilitic lesions were prominent, and the authors therefore suggest that chronic syphilitic lesions of the aorta predispose to the development of local atherosclerosis.

Coronary Insufficiency and Coronary Occlusion.

ARTHUR H. MASTER, H. H. CARROLL AND CECIL ANDREWS (*United States Naval Medical Bulletin*, October, 1942) discuss the incidence, symptoms and signs, pathology, prognosis and differential diagnosis of coronary insufficiency and coronary occlusion. Coronary disease appears to be increasing, but an increasingly greater percentage of the population is living to attain the higher age groups, the medical profession is becoming "coronary disease conscious", and recent advances have made the diagnosis easier and more accurate. Stress is laid on the marked difference in duration and prognosis of the two conditions, coronary insufficiency being a prolonged ischæmia of the heart muscle, with necrosis, but without occlusion of the coronary artery. The latter condition completely obstructs the coronary flow and gives myocardial infarction, whereas in coronary insufficiency there is disproportion between the work of the myocardium and the coronary blood flow. Pathologically, the artery is always diseased before occlusion, but it may be normal in ischæmia, although some degree of sclerosis is a predisposing cause. There are no exciting causes of coronary occlusion, but many of coronary ischæmia. In the latter condition, duration is much less and prognosis is better, whilst in coronary occlusion a fatal outcome is not uncommon, and in some cases eventually the fatal period of incapacity may last for months. In a period of four weeks in a 250-bed hospital, nine cases of coronary insufficiency and six cases of coronary occlusion were studied fully, and complete investigations are recorded.

Functional Heart Disease.

W. G. MITCHELL (*United States Naval Medical Bulletin*, October, 1942) has analysed 100 cases referred to the cardiac clinic following routine examination of recruits for naval aviation. Recruits with the more obvious and disabling heart conditions had already been eliminated, and the majority examined by the cardiologist were referred to the clinic because of a heart murmur or arrhythmia, whilst the greater number of men had no complaints and were surprised to be under consideration for heart disease. The method of examination is described, and the Schneider index was used to compute cardiac efficiency. Of the subjects seen, 80% were considered to be suffering from a functional condition and were passed for flight training. X-ray examination and electrocardiography were rarely necessary in arriving at a correct opinion in cases in which the only abnormality was a murmur, but were of value chiefly in congenital heart disease for the evaluation of the murmur and the anatomical abnormalities. The majority of systolic murmurs in this age group were physiological, but there is a possibility that certain benign arrhythmias may pass into a more serious state when the individual is under stress and nervous tension.

Medical Societies.

THE PUBLIC MEDICAL OFFICERS' ASSOCIATION OF NEW SOUTH WALES.

THE annual general meeting of the Public Medical Officers' Association of New South Wales was held at the British Medical Association House, 135, Macquarie Street, Sydney, on January 28, 1943. Dr. A. T. Edwards, the President, occupied the chair and 26 members were present. Seven members appointed proxies to vote for them, five of which were accepted as valid.

Financial Statement.

The Honorary Treasurer, Dr. C. E. Percy, presented his financial statement which showed receipt of £28 8s. 11d. and disbursement of £4 18s. 1d during the year 1942. The accumulated surplus was £589 5s. 3d., of which £550 was invested in war loans.

Annual Report of the Committee.

The Honorary Secretary presented the committee's annual report. It read as follows:

1. During the year 1942, as in recent years, the war situation obliged the Association to continue to restrain its activities.

2. There are now 107 members of the Association, of whom 28 are life members, and 11, having retired from the Services, are retained as honorary members. The decline in membership is due to deaths and resignations from the Services which have not been balanced by new entrants because of cessation of recruitment during the war. In a few cases membership has been cancelled because subscriptions were in arrear.

3. The committee met six times during the year, attendances being: Dr. A. T. Edwards (President), 6; Dr. S. Evan Jones, 5; Dr. Dorothy McClemens, 5; Dr. C. E. Percy, 5; Dr. J. McManamey, 3; Dr. G. C. Smith, 5; Dr. H. M. Taylor, 1; Dr. H. H. Willis (Secretary), 6. Dr. Hilliard was elected to fill a casual vacancy during the year, but did not act.

4. The desirability of admitting to membership foreign graduates in the Services who hold Federal licences to practise, but are not registered under State law, has received attention by the committee and an instruction from an annual general meeting is sought.

5. Relations with other Service organizations and with the British Medical Association remain cordial. The threat of revolutionary changes in medical practice makes cooperation with the British Medical Association even more necessary than in the past, and it may be necessary for members to decide in the near future whether they desire anything more than the loose nexus which has existed between the two Associations in the past.

6. As instructed by the annual general meeting of January, 1942, the committee has continued to seek better working conditions in mental hospitals and especially to obtain a less harsh interpretation of Regulation 152 concerning so-called "Privilege Leave". It early became apparent that an approach along the lines dictated by the annual meeting would not be advantageous, but by indirect negotiation some amelioration has been effected. It is hoped that shortly a settlement of this prolonged dispute reasonably satisfactory to our members will be reached.

7. The system of promotion in the Services is a matter of increasing importance in view of the possible introduction of a salaried national medical service in the near future. It is suggested that the Association formulate a policy on this matter and as a basis for discussion the following two points are submitted as essential features of a satisfactory system: (*a*) An appeal board to which unsuccessful applicants for promotion might appeal, and (*b*) selection for promotion to be primarily by efficiency and secondarily by seniority, whether that seniority be determined by salary or length of service.

Election of Office Bearers.

The election of office bearers for 1943 resulted as follows:

President: Dr. Sybil Bevan.
Honorary Secretary: Dr. H. Hastings Willis.
Auditor: Dr. S. McGeorge.
Committee: Dr. C. E. Percy, Dr. J. McManamey and Dr. G. C. Smith (New South Wales Health Department), Dr. S. Evan Jones and Dr. A. T. Edwards (Mental Hospitals), Dr. Dorothy McClemens and Dr. Edelsten Pope (Education Department), Dr. H. M. Taylor (Works and Railways), Dr. H. H. Willis (Repatriation Department).

Rules of the Association.

The rules of the association were altered to make licensed medical practitioners eligible for membership as if they were legally registered, provided they are of British nationality and not of enemy origin.

An amendment to omit the words "not of enemy origin" was lost by 17 votes to 10.

Medical Convention of the Future of Medical Practice.

It was decided to accept an invitation from the President of the New South Wales Branch of the British Medical Association to send a delegate to a medical convention in Sydney on February 5, 1943, and Dr. H. Hastings Willis was chosen for that purpose.

A motion moved by Dr. S. Evan Jones and seconded by Dr. A. T. Edwards, "That a salaried medical service is in the best interests of the public and the profession", provoked a long discussion and was finally carried by 14 votes to 7. An amendment favouring a "fee for service" system and another favouring a "capitation" system were lost by large majorities.

A motion by Dr. Evan Jones and Dr. Noel Kirkwood "That a national health scheme should be comprehensive and include specialist, hospital, general practitioner and public health services" was carried unanimously.

It was decided to ask that the following motion in the name of the association be placed on the agenda of the convention: "That all hospitals should be controlled by a national medical service."

Votes of Thanks.

The meeting closed with a vote of thanks to Dr. Sybil Bevan who had been inducted as President for 1943, and to the retiring President, Dr. A. T. Edwards.

Correspondence.

A SCHEME FOR A MEDICAL SERVICE FOR THE COMMONWEALTH.

SIR: I have read with interest the various contributions in THE MEDICAL JOURNAL OF AUSTRALIA to the consideration of an amended scheme of medical service to the community, particularly the article by Dr. Davis in the issue of the 13th instant.

It is particularly interesting to note the gradual realization that a scheme of social security, national insurance or a scheme by any other name does not necessarily require the incorporation of the medical profession, but so far I have failed to see any basic principles presented.

Before the profession presents to the community a scheme of medical services, saying, "here is the cure for our present shortcomings and the preventive against future ones", I trust that every use will be made of the function of clear thinking—about which the profession as a whole must have much physiological (and pathological) knowledge, and that the profession will then present a set of basic logical principles.

I think Dr. Davis is to be congratulated upon his meticulous attention to detail, and it is to be hoped that when the basic principles of a satisfactory scheme have been established some of the suggestions made by Dr. Davis will take their deserved place in the detail of the scheme.

Singer has castigated Galen as a horribly efficient man who was willing to dispense the type of "medicine" demanded by the civic powers of his day in the manner demanded instead of insisting upon supplying the type of "medicine" his experience should have taught him was needed. To avoid this trap—and this appears to be the essential temptation the medical profession fears today—will require all the determination, unity, loyalty, fidelity and work the profession is capable of. Might I suggest that the time is opportune to commence at the beginning and to pay some attention to the historical method of consideration before further confusing the issue by discussing detail before

principle. This might be done with the realization that "principles" built upon a mass of irrelevant detail will be wafted away with the first breath of sweet reason, while detail flowing from basic logical principles will stand the test of trial, suspicion, contempt, and even hatred and disloyalty and finally time, and lead to the ultimate aim of all scientific planning, namely, simplification by better understanding.

As a first instalment to the "historical method" some thought might be given to the "progress" since the day when the Church dispensed legal, medical and spiritual advice without "lay" interference to the present day of "specialization", when we find these three functions entrusted to three separate "practitioners". (Remembering, of course, the very real difference between legitimate and necessary constructive criticism and mere interference.)

We are all familiar with the lay committee of the local hospital and the various lay church committees and with the "quack" medical practitioner and even with the occasional "quack" preacher, but we have yet to hear of a "quack" lawyer or of a "local court committee" passing judgement upon complaints made by the court keeper against the behaviour of the presiding judge, or deciding the type of justice to be administered to the community.

Might this not suggest that we could look with advantage to the organization dispensing legal advice and "treatment" to learn where our downfall commenced and thus commence with a logical appreciation of the basic principle of our problem.

I use the word downfall deliberately, for I could never imagine a people physiologically satisfied with a medical service they are now receiving permitting the most energetic or dynamic personality even suggesting a radical change.

Few can be at variance with Singer in his criticism of Galen when we realize that while the populace might dictate advisedly their more material wants (blue hats or green shoes), the supply of less easily definable more immaterial wants must be left to those with the necessary knowledge and experience to educate the populace as to its needs. The day the medical profession commences to supply a medical service contrary to that needed by the populace will surely be the day the profession commences to earn, deserve and receive the scathing criticism Singer has offered to Galen's memory. If the medical profession has been educated in and has conscientiously developed the true functions of the medical practitioner, the prevention of any such catastrophe is in the hands of the medical profession itself.

Once the medical profession presents a planned, scientific scheme for an amended form of medical service there should be no adequate reply but one of acceptance when one recalls the knowledge, experience and material at the command of a profession versed in the principles and interpretation of "natural laws".

Is it yet too late to form a study group with the object of presenting to the nation a logical planned system of medical services—one which does not confuse provision with supply nor security with freedom?

While a scheme of medical services propounded on the miserable basis of expediency might be

> Like a ship at sea, carrying with full sail a load
> of little weight,
> Only new ideas and untried experiments,

the ship need never sail if appropriate action follows the message to the nation that

> You who have been so long my friend, have guessed
> The store of salvaged treasure I have drained
> From every failure, till at last remained
> Only the essence of each trammelled quest.

Yours, etc.,

44, Northcote Road,
Lindfield,
New South Wales.
March 14, 1943.

I. A. D. GRAHAM.

FEWER MEDICAL STUDENTS.

SIR: In your issue of Saturday, March 20, you point out various anomalies in the matter of limiting and selecting students to be admitted to the Faculty of Medicine. But why, may I ask, should there be any interference at all?

As a medical man, I have worked in many hospitals, and I have had university experience. And I have never seen any single reason for complaint in the present system, whereby the students accept their own responsibility for the quality of their work, their conduct, and for student representation on the various governing bodies.

In my first year at the Melbourne University there were more than 200 medical students. We had a good time, and I think our work was as good as the lecturers demanded and expected. Our best student, after taking most of the prizes, married and left the university to take up aviation. One of our poorest students has contributed some of the best medical and other research seen for a long time.

Why not leave well alone?

Yours, etc.,

Kalorama,
Victoria,
March 25, 1943.

J. L. WHITWORTH.

REMOVAL OF PLASTER CASTS.

SIR: Perhaps some further elucidation of this difficulty is desirable in view of the full condemnation of the tube method, associated with the name of A. T. Andreason, by John Dick, in THE MEDICAL JOURNAL OF AUSTRALIA, March 27, 1943.

Having had no significant disability from tubing methods in extensive use for about two years, and having found it effective and perhaps the most practical routine in nearly all types of plaster work other than a few particular procedures requiring extreme accuracy of retention, I think the following should be kept in mind along with the possible disadvantages rightly pointed out by John Dick.

As regards the scarcity of rubber, we have during this period not had occasion to replace the one original tube, nor has that tube been shortened. The amount of rubber in our experience is therefore insignificant, and there is probably greater gain in other directions.

I agree with him that old rubber liable to snap should not be used. With reduction of friction by the application of suitable emollient to the tubing there is no undue strain upon good quality rubber, and I have not seen any tubing snap. If tubing did snap due to poor quality rubber or other factors, no damage would be done to the patient and the piece of tubing would be readily recovered.

It is with his third contention that I am chiefly concerned. In this he refers to the dead space into which he has seen a bulging œdema with blistering of the skin throughout the whole length of the tunnel and he records a case of cellulitis associated with this condition. I would regard this rather as the result of a faulty technique than primarily due to the method. There should be a flooring to the tunnel in continuity with the inner surface of the rest of the plaster. This can be obtained in several ways. Where the circumstances allow of a tubular bandage covering on the skin this in itself is generally efficient in preventing any significant œdema into the tunnel, forming as it does a flooring across the base. It is better, however, as a rule, to use a thin piece of felt about one and a half inches wide over the tubular weave which becomes stretched across the base of the tunnel as the plaster dries, forming an effective barrier against œdema and adding to the comfort of the patient by avoiding contact of the sharp point of the cutting blade against the skin. Though I do not myself use skin plasters, the method can still be used in such a procedure by the use of a strip of the same width adhesive felt, in the position of the tubing. This adhesive felt is also quite firmly held by the plaster as a flooring for the tunnel.

The method in any case is not applicable under all circumstances, and should not be completely condemned because it is not universally applicable. It is probably better not used in a very small portion of cases where for some particular reason absolute immobility is desirable, but this proportion of cases becomes very small if the tube be used over the soft parts, leaving subcutaneous bone for close plaster coaptation for maintenance of position.

Yours, etc.,

STUART SCOUGALL.

British Medical Association House,
137, Macquarie Street,
Sydney.
April 5, 1943.

AN EASY WAY OF ISOLATING A HERNIAL SAC AND THE USE OF COTTON AND LINEN SUTURES.

SIR: Dr. Edward Hanly, in his letter of March 27, 1943, has raised the question of technique in operating on inguinal hernia.

I thought that Rodney Maingot had almost settled this question in his article on hernia in "Post-Graduate Surgery". However, Dr. Hanly seems to have altogether missed, and even Rodney Maingot does not sufficiently stress the secret of prevention and cure of hernia of the anterior abdominal wall. This seems to me to be repair or replacement, with non-absorbable sutures, of the transversalis fascia. The importance of this layer first struck me, many years ago, when closing mid-line suprapubic incisions according to the usual method. I always felt most unhappy about that flabby and apparently redundant layer of peritoneum, which was left in the floor of the wound, and which bulged so grotesquely if the patient coughed at this stage of the operation. I began then, and have always continued since, to suture carefully the transversalis fascia in this and any other incision through the anterior abdominal wall.

I have come to regard the transversalis fascia as Nature's first and most important defence against hernia, and have regarded the muscle layers as mobile reserves, which are useful only if their normal position and function are preserved. This principle, applied to the treatment of hernia, has always given good results, and is really the foundation of the Maingot technique. Success with the Bassini technique seems to me to depend on: (*a*) Luck or the "Divinity that shapes our ends". (*b*) The fact that, in freeing the sac, one often leaves strands of internal spermatic fascia attached to it. These are included in the ligature encircling the stump and so provide a barrier across the gap in the transversalis fascia.

I realize that there is normally an inevitable gap in the transversalis fascia at the abdominal inguinal ring. It occurs to me that Nature provides for filling this gap and the inguinal and femoral canals by distension, with increased intraabdominal pressure, of the internal spermatic vein, the pampiniform plexus and the femoral vein respectively. There seems to be a nice problem in mechanical and hydraulic engineering here, worthy of analysis by Dr. C. E. Corlette.

Finally I commend to anyone a study of Plate ix facing page 258 in Volume II of Cunningham's "Manual of Practical Anatomy". This picture represents what might be called a "gut's-eye view" of the transversalis fascia. It almost suggests that Nature intended that any abnormal gap in the fascia should be darned by interlacing transverse and longitudinal strands of non-absorbable suture material. Q.E.D.

Yours, etc.,

D. M. STEWART.

East Maitland,
New South Wales,
April 5, 1943.

A CORRECTION.

SIR: Owing to an error in transcription I attributed to Dr. F. Blois Lawton a statement that potassium chloride could not be used in considerable doses. The observation applied to other salts of potassium.

Hay fever is obviously a fundamental and biochemical condition. It occurs in people of advancing years who did not have it earlier. It is relieved in many cases by zinc ionization of the nose. Its cause is apparently unknown because in many cases the most elaborate attempts to find out any change which excites it fail.

It may be that potassium chloride in varying quantities may give more relief than it has in the smaller doses.

Yours, etc.,

JAMES W. BARRETT.

103-105, Collins Street,
Melbourne,
April 15, 1943.

WORDS.

SIR: Despite the efforts of the Prime Minister, A. P. Herbert and others, the introduction of new and barbaric phrases in medical literature is growing steadily.

The other day I came across "advisement" in a leading American surgical journal, and the last is the clumsy phrase "no osseous lesion detected" (contracted to N.O.L.D.) of the radiologist. The prudery and inaccuracy of "void" for "pass" is, I fear, beyond hope, but, "no osseous lesion detected" (why not "no bony injury seen")—can we not stop the infection spreading? But my tilt at medical journalese is not purely academic. At present many doctors are writing medical reports which are of very great importance as permanent records of disease in a large part of our population. These records are being transcribed by men and women whose education is limited, and one has only to work through some of the transcribed records to see how badly mauled the most elegant phrases may become in transit. I make no plea for clearer writing by doctors—that (*peccavi—multum peccavi*) is past praying for—but I do ask that the simple and more familiar word may always be used—despite a temptation to follow the late James Pinkerton in his love of "boss words".

Yours, etc.,

S. F. MCDONALD.

Craigston,
217, Wickham Terrace,
Brisbane.
April 10, 1943.

THE FUTURE OF MEDICAL PRACTICE.

SIR: Much discussion has taken place on the above subject, and it might serve some useful purpose to try and sum up the present position.

In my view there are two important results already apparent: (i) The general agreement that some improvement in the conduct of medical practice from present-day methods is necessary. (ii) The willingness of the profession to adapt itself to altering conditions.

The profession has shown that it prefers to be allowed to control itself from within, rather than from without. It also appears to have been established that the salaried service proposed was too unwieldy to function, and needed a considerable modification. The Hospital Commission Committee appointed to look into all hospitals should do much good work and will be welcomed. It would be well to remember that our present system has been built up partly under an order which has allowed greed and selfishness to have too much play, and as a new and more humane order evolves, the medical profession can be trusted to readily fit into any improved social set-up, provided the rank and file are given adequate representation.

Yours, etc.,

H. T. ILLINGWORTH, M.B., Ch.M.

Bruce Rock,
Western Australia,
April 8, 1943.

SIR: Will you allow me space in your journal to bring forward some aspects of national health?

At a recent convention in this State many admirable and necessary improvements in medical practice were formulated and suggestions put forward which should do much to advance our work in safeguarding and maintaining the health of the people. Stress was rightly laid on the improvement of housing and living conditions generally and the very important factor of nutrition received attention. Further facilities for hospitalization and for diagnostic aids were also fully covered.

It appears to me, however, that too much stress has been laid on the subject of disease and too little on that of health.

In recent years clever advertising and the popularity of disease as a subject for newspaper articles, novels and public comment have tended to make the community disease conscious—a fact which would be very much increased by a national medical service. It is quite fallacious to suppose that any form of medical service will bring about marked improvement in national health. It is far more likely to produce a nation of hypochondriacs, fear-ridden by the terror of illness.

National health can be best attained by cultivating a health consciousness, and this can only be brought about by means of a carefully planned system of education. The results of such a campaign would not immediately become apparent, but posterity would reap the benefit of our foresight.

This subject may be considered under two headings: (*a*) education of the community, (*b*) education of the individual.

(*a*) *The Community.*—Firstly, all advertising (newspaper and radio) which mentions disease and/or its treatment should be prohibited. Instead, health propaganda prepared by a committee of experts should be substituted—something on the lines of the present health week, but continued throughout the year. Opportunities for rest and recreation should be increased and the community educated to make

the most healthful use of recreation times. The increasing tendency is towards the shortening of hours of work, and in addition provision should be made for yearly holidays for all workers and on full pay. But these increased recreation times should be utilized to the best advantage and full health value obtained. This will require adult education, and encouragement in the cultivation of hobbies or other provisions for both mental and physical relaxation.

(*b*) *The Individual.*—The present education system prepares children to earn a living, perhaps adds a little general culture, but makes no attempt to teach them how to live. This appears to me to be a serious omission, and to repair this biology should be made a compulsory subject in schools. The inanimate sciences are now more favoured, but an understanding of the processes of life and a realization of simple physiological facts would place the child on a firm foundation for a healthful future. Even an elementary knowledge of health and hygiene would aid towards success in living and that these subjects should be taught early is fundamental. In this way the child would grow up with some appreciation of natural health. The reproductive function could then be made to assume its correct biological significance, along with the digestive, respiratory and excretory functions, as merely one of the four great functions of all living things. The advantages of thus tearing down the curtain of mystery are obvious.

I do not wish to trespass to an undue extent on the space available for correspondence nor to go into further details. My wish is more to indicate an opportunity, which should be exploited, to give this country, needing manpower so sorely, a healthy, happy people. And perhaps to suggest additional avenues of thought to those who are striving for improved national health.

How these reforms are to be implemented is not for this letter, but for an educational conference with medical representation.

Yours, etc.,

M. H. ELLIOT SMITH.

Mosman,
New South Wales,
April 9, 1943.

SIR: In my opinion: (i) This is no time to stir up controversy and waste time and money. (ii) There is not much wrong with the present system. (iii) The most formidable advocates of a change know very little about medical practice.

Enlarging a little:

1. We are told to subject everything to the war effort, to give or lend every penny, and that "nothing matters now but victory". I agree, but somebody in authority has his fingers crossed when endorsing such noble sentiments and at the same time planning a medical revolution. Practising doctors simply have not time or opportunity to take an interest. They are all working too hard—directly or indirectly—for victory. Our attitude should be one of passive (or active) resistance, and Sir Henry Newland's refusal to attend a certain meeting was exemplary.

2. I know little of specialist, city or large lodge practice, but country service is good. Workers' compensation, lodge and social service lists ensure adequate care of most of the poorer people without undue exploitation of the doctor, who, however, gives willing free service to the few strays who are not provided for. Anybody at all can be sent to city specialists without cost if necessary. The only difficulty is in getting specialists to the patients, and this would be simply overcome by the Government subsidizing visits by various specialists rarely, and by pathologists and radiologists regularly. The greatest problem of all is the early tuberculosis case. It is a fact that proper accommodation often cannot be obtained under several months, necessitating waste of this valuable time in their own home (infecting other people) or in a public hospital (where they are not allowed by the rules), and in any case in an unsuitable climate. Here indeed is a chance for some money spending—even in wartime. General practice in the country is satisfactory, and the standard of work and ability improves every year. The standard is a good deal higher than many people imagine.

3. Sir Raphael Cilento at Brisbane (THE MEDICAL JOURNAL OF AUSTRALIA, April 10, 1943) was "amazed" at several things including the criticism regarding free choice of doctor. The patient in a one man town, he said, has no free choice. (There are eleven one man towns within sixty-five miles of Parkes, and the amount of free choice exercised would "amaze" anybody.) The patient in the city, he said, was limited by distance and cash. (This surely cannot apply to a great extent, and anyhow, it should be cured by Dr. Streeter's suggestion of adjusting the cash!) Distant country patients, he said, might well desire to consult men in . . . Macquarie Street. (They do if necessary, whatever their finances, maybe travelling by special stretcher in a guard's van, or on a free pass or in an ambulance.) Many a man, he said, would like to consult one or other of the sixteen men in his own suburb . . . but he had to go to his lodge doctor. (Well, he chose the lodge doctor.) The Council proposed, he said, that the patient should be able to go to any one of the . . . sixteen doctors. (So he may, now, but I know many who would, under the scheme, go to all of them within a year and get nowhere—recounting the minor conversation of each one to each other one!) In an emergency, he said, the patient would be restricted in his choice, as was the case in all circumstances. (The latter is not correct. The seriously ill or injured patient is usually emphatic about which doctor he sees, partly because the one he knows will take a more intense and personal interest; and in the country he usually succeeds in seeing him.) Domiciliary services, he said, would be provided from the clinic, with the assistance of juniors allocated. (Many a dear old lady would die unattended.)

With the greatest respect to Sir Raphael Cilento, I suggest that his knowledge of medical practice is limited, and that continuity of service is perhaps the most important thing in medicine.

This idea explains the fact that in certain respects some small hospitals are better than larger ones. The very sick patient is continuously the responsibility of and under the supervision of one nurse and one doctor, without people popping on and off duty all the time and nobody knowing anything!

By all means let us emulate Sir Henry Newland and oppose this thing, at least for the duration, utterly and completely.

Yours, etc.,

G. B. DOWNES.

Parkes,
New South Wales,
April 13, 1943.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 76, of April 8, 1943.

ROYAL AUSTRALIAN AIR FORCE.

Citizen Air Force: Medical Branch.

The Probationary Appointment of Flight Lieutenant (Temporary Squadron Leader) L. H. Albiston (6799) is confirmed.

The probationary appointment of Flight Lieutenant C. R. Laing (3407) is confirmed.

Samuel Lockington Strange, M.B., Ch.B., D.T.M., F.R.C.S. (287407), is appointed to a commission on probation with the rank of Flight Lieutenant with effect from 26th February, 1943.

Flight Lieutenant John Bryant Curtis, M.B., B.S. (7233) is transferred from the Medical Branch Reserve for full-time duties with effect from 1st March, 1943.

Mortimer Zilko, M.B., B.S. (297402), is appointed to a commission on probation with the rank of Flight Lieutenant, with effect from 22nd February, 1943.

Reserve: Medical Branch.

The following are appointed to commissions on probation with the rank of Flight Lieutenant with effect from 26th February, 1943: Robert Thornborough Steele, M.B., B.S. (287406), William Thomas Whitby, M.B., B.S. (267407), Malcolm Bell, M.B., B.S. (267408), John Paul Gallagher, M.B., B.S. (267409), Courtenay Warwick Whitelaw, M.B., B.S. (267410), Winston Parker-Smith, M.B., B.S. (267411), Arthur Dudley Packer, M.B., B.S., B.Sc. (287403), Kingsley Clarence Porter, M.B., B.S. (287404), Cyril David Swaine, M.B., B.S. (287405).—(Ex. Min. No. 88—Approved 7th April, 1943.)

Neville Beresford Howse, M.B., B.S. (267413), is appointed to a commission on probation with the rank of Flight Lieutenant, with effect from 1st March, 1943.—(Ex. Min. No. 89—Approved 7th April, 1943.)

Australian Medical Board Proceedings.

NEW SOUTH WALES.

THE undermentioned have been registered, pursuant to the *Medical Practitioners Act*, 1938-1939, of New South Wales, as duly qualified medical practitioners:

Dick, John Chesterton, L.R.C.P., L.R.C.S. (Edinburgh), L.R.F.P.S. (Glasgow), 1939, F.R.C.S. (Edinburgh), 1941, 7, Benelong Crescent, Bellevue Hill.

Rodriguez, Phyllis Edna, L.M.S., 1937 (Singapore), 98, Henley Beach Road, Mile End, South Australia.

Jury, Leslie Ronald, M.B., B.S., 1939 (Univ. Sydney), 2nd A.M.C. Training Battalion, A.I.F.

The following additional qualifications have been registered:

Balzer, John Camfield, M.B., Ch.M., 1926 (Univ. Sydney), F.R.C.S. (England), 1935, 23, Hopetoun Avenue, Mosman (A.I.F.).

Grant, Alan Mostyn Bradford, M.B., B.S., 1929 (Univ. Sydney), F.R.C.S. (Edinburgh), 1935, Waverley.

Dowling, Heather Daphne, M.B., B.S., 1933 (Univ. Sydney), D.M.R.C. (Cambridge), 1938, 7, Benelong Crescent, Bellevue Hill. (Name now changed to Dick, Heather Daphne.)

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Cranswick, Edward Harvard, M.B., B.S., 1940 (Univ. Sydney), Captain, Australian Army Medical Corps, Australia.

The undermentioned have been elected members of the New South Wales Branch of the British Medical Association:

Abbott, Jack Henry Palmer, M.B., B.S., 1942 (Univ. Sydney), Newcastle Hospital, Newcastle.

Fiaschi, Elisa Berta Alexandria, M.B., 1939 (Univ. Sydney), King George V Memorial Hospital, Camperdown.

Lawrence, Lorraine Cecile, M.B., B.S., 1942 (Univ. Sydney), 11, Milray Avenue, Wollstonecraft.

McGirr, John Joseph Gregory, M.B., 1942 (Univ. Sydney), Mater Misericordiæ Hospital, Waratah.

Mulvey, Margaret, M.B., B.S., 1940 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.

Murray, Victor Reginald Ernest, M.B., B.S., 1941 (Univ. Sydney), Balranald.

Royle, Norman James, M.B., B.S., 1940 (Univ. Sydney), "Moola", Pittwater Road, Pymble.

Denneen, Alan Thirlwall, M.B., B.S., 1936 (Univ. Sydney), Macquarie Cottage, Argyle Street, Picton.

Holt, Ian Wellesley, M.B., B.S., 1939 (Univ. Sydney), 2, The Appian Way, Burwood.

Medical Appointments.

Dr. Alexander Jamieson Meikle has been reappointed to be an official visitor to the Mental Hospital, Parkside, South Australia.

Dr. Rupert Eric Magarey has been appointed temporary honorary associate gynæcologist at the Royal Adelaide Hospital, Adelaide, South Australia.

Dr. Carl Helman has been appointed temporary honorary assistant anæsthetist at the Royal Adelaide Hospital, Adelaide, South Australia.

Dr. Freda Evelyn Gibson, pursuant to the provisions of the *Health Act*, 1935-1941, of South Australia, has been appointed Deputy Officer of Health at and around Fowler's Bay, Penong, Cook and Tarcoola, South Australia.

Dr. Francis James Ryan has been appointed Acting Deputy Superintendent, Northfield Mental Hospital, South Australia.

Books Received.

"Medical Ethics", by Rupert M. Downes, C.M.G., V.D., M.D., M.S., F.R.A.C.S.; 1942. Melbourne: W. Ramsay (Surgical) Proprietary Limited. 8¼" × 5¼", pp. 78. Price: 5s.

Diary for the Month.

MAY 4.—New South Wales Branch, B.M.A.: Organization and Science Committee.
MAY 5.—Victorian Branch, B.M.A.: Branch.
MAY 5.—Western Australian Branch, B.M.A.: Council.
MAY 6.—South Australian Branch, B.M.A.: Council.
MAY 7.—Queensland Branch, B.M.A.: Branch.
MAY 11.—Tasmanian Branch, B.M.A.: Branch.
MAY 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
MAY 14.—Queensland Branch, B.M.A.: Council.
MAY 18.—New South Wales Branch, B.M.A.: Ethics Committee.
MAY 19.—Western Australian Branch, B.M.A.: Branch.
MAY 20.—New South Wales Branch, B.M.A.: Clinical Meeting.
MAY 25.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAY 26.—Victorian Branch, B.M.A.: Council.
MAY 27.—New South Wales Branch, B.M.A.: Branch.
MAY 27.—South Australian Branch, B.M.A.: Branch.
MAY 28.—Queensland Branch, B.M.A.: Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

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